Oral Mucositis: a nurse's perspective

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Als je doet wat je leuk vindt,
hoef je nooit te werken.
Mahatma Gandhi

Oral Mucositis: a nurse's perspective

een wetenschappelijke proeve
op het gebied van de Medische Wetenschappen

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Chapter 1

General introduction

Introduction

In the Netherlands, approximately 74.500 patients will be diagnosed with cancer every year. Hence, 2.5% of the Dutch population will be treated for cancer[1]. Many types of cancer can be treated effectively with chemotherapy, radiotherapy or a combination of both. Unfortunately such therapy affects all rapidly dividing cells whether neoplastic or not. Consequently, the lining of the oral cavity is at high risk of side effects. Mucositis is the medical term that is used to refer to oral complaints that can range in severity from a red, sore mouth to open sores that can be severe enough to prevent eating and drinking. A basic definition of mucositis is the development of erythema and ulceration of the mucosa following chemotherapy with or without irradiation for treating cancer[2]. Oral mucositis markedly influences the physical and psychosocial wellbeing of patients undergoing cancer therapy. As oncology nurses play a critical role in improving patient outcomes related to oral mucositis [3], knowledge and research regarding oral mucositis forms a crucial part of their activities.
Managing oral mucositis is as important as managing, fatigue, nausea and vomiting, and many other side effects that affect patients with cancer. Oral mucositis is one of the most frequent causes of treatment delay and dosage reductions in cancer therapy[2].
Patients' quality of life can also be affected markedly by pain, infection, altered nutrition, and decrease in oral function[4, 5].

Incidence

The incidence of oral mucositis varies widely based on the specific type of cancer and the modality used for treatment. Mucositis often is associated with radiotherapy of head and neck cancer and with high-dose cytostatic chemotherapy regimens, especially those used in haematopoietic stem cell transplantation. According to Elting and colleagues[6] mucositis also occurs with the use of myelosuppressive chemotherapy for solid tumours. Epstein and Schubert[7] found that 30%–75% of chemotherapy patients experienced oral mucositis. The frequency associated with head and neck radiotherapy and haematopoietic stem cell transplantation exceeds 90%[8].

Pathology

Sonis[9] postulated that the pathobiology of oral mucositis consists of five phases (see Figure 1).
The first phase is initiation which occurs immediately after radiotherapy or chemotherapy is delivered. Direct damage to the epithelial cells injures the DNA and results in the death of a small fraction of cells.
The second phase of the oral mucositis model is upregulation and message generation. During this phase of oral mucositis, multiple events are known to occur simultaneously.

Inflammatory cytokines are released that cause further tissue injury and cell death. The mucosa starts to thin, and erythema may be present. Tumour necrosis factor-alpha (TNF-α), a proinflammatory cytokine, is a protein produced by monocytes and macrophages that is increased because of inflammation. TNF-α has the ability to cause necrosis by interfering with blood flow, it induces cytotoxic inflammation, and regulates the immune responses.

The third phase is signalling and amplification, which consists of direct damage to cells and escalation of the process initiated by proinflammatory cytokines. In this phase, TNF-α activates additional cytokines, creating a feedback loop that enlarges the biological effects. Most of the damage occurs below the level of the mucosa.

During the fourth phase, the ulceration of oral mucositis is the most significant to both patient and caregiver. Loss of mucosal integrity produces lesions that can be extremely painful. Breaks in the mucosal epithelium may provide portals of entry for bacteria, viruses, and fungi located on the surface. Bacterial cell wall products induce immune cells to produce cytokines, leading to further inflammation and apoptosis.

Healing forms the final phase when the epithelial cells that border the ulcer begin to migrate into the wound bed where they proliferate. The tissue will start to form layers, and the normal oral microbial flora will re-establish itself.

Figure 1: *Phases of Mucositis*

Phase 1	Phase2	Phase3	Phase4	Phase5
Initiation	Upregulation and message generation	Signalling and amplification	Ulceration	Healing

Based on Sonis 2004

Clinical presentation of oral mucositis

Some patients treated for cancer never develop oral mucositis, and not every treatment causes oral mucositis. Patterns of oral mucositis vary with the type and dosage of cancer therapy[10].

The dose, intensity, duration, and frequency of chemotherapy administration increase the risk for oral mucositis. Ulceration among patients who develop oral mucositis following stomatotoxic chemotherapy tends to become clinically apparent about one week after treatment and severity generally progresses to a peak roughly 14 days after the start of therapy. Healing will occur within 2-3 weeks after chemotherapy is ended[7].

After chemotherapy, mild erythema and oedema of the oral mucosa develops first, followed by dryness of the mouth and a burning sensation in the lips. Ulcerations occur at the lateral and ventral tongue, buccal mucosa, and soft plate. The ulcerative stage is painful and affects nutritional intake while speaking becomes difficult [11]. Severe pain often requires opioid intervention[12]. Chronic pseudomembrane can also be present, with dry, red buccal mucosa and a reddened, swollen, shiny, dry, cracked tongue[13].

The degree and duration of oral mucositis in patients who receive head and neck radiation therapy are influenced by the radiation source, cumulative dose, dose intensity, and volume of radiated tissue or fractionation[14]. Patients who receive head and neck radiation therapy tend to develop erythema during the second week of therapy in conjunction with a total dose of approximately 2,000 cGy and symptoms peak around the fifth or sixth week of radiation therapy. Severity increases as the dose increases, with the worst mucosal reactions associated with total doses ranging from 5,000–6,000 cGy[15]. Healing then takes approximately 2-3 weeks[16]. It is not uncommon for patients receiving radiotherapy for cancer of the month to have severe ulcerative oral mucositis for 5-7 weeks[12]. As with chemotherapy-induced mucositis, that seen with radiation therapy initially presents as redness and swelling. The mucosa then becomes denuded, ulcerated, and covered with a white pseudomembrane. Lesions are limited to tissues in the field of radiation [11]. Pain, burning, and discomfort are felt, swallowing and speaking become difficult. Reduction in salivary flow is related to the dose and duration of radiation therapy[13].

An oral assessment is an important first step in the management of oral mucositis and objective (erythema, lesions, oedema), subjective (pain or sensitivity, dryness), and functional aspects (voice, swallowing, chewing) need to be taken into account.

A major obstacle to mucositis research has been the lack of an objective scoring system for mucositis that is universally accepted. Instead, individuals and groups have developed a variety of different scoring systems, often with different objectives.

The management of oral mucositis

Nurses are the primary advocates for patients, and play a central role in preventing and managing oral mucositis and reducing its burden on patients. Oral care is an essential component of an oral mucositis management programme.

Assessment

Assessment of oral mucositis is the first step in the nursing process. The primary goal of the nursing assessment of the oral cavity is to identify changes in the oral mucosa, recognize the presence of infection, and describe the effect that oral mucositis has on patients' functional status. Using systematic, regularly scheduled oral assessments with a reliable and valid rating scale specifically designed to assess oral mucositis among patients with cancer will allow oncology nurses to better recognize, monitor, and document the progression of oral mucositis and institute nursing interventions to ease patients' discomfort[3]. The scale adopted by the World Health Organization (WHO) is the most widely used and was developed to describe toxicities associated with a particular chemotherapeutic regimen or radiation therapy. The WHO scale addresses all three components of oral mucositis: objective signs (such as ulceration), subjective

Grade 1:
Soreness and erythema

Grade 2:
Erythema and or lesions; patient can swallow solid diet

Grade 3:
Lesions with or without extensive erythema; patient is able to swallow liquid but cannot swallow solid diet.

Grade 4:
Mucositis to the extent that patient is not able to tolerate even liquid diet.

http://www.cdc.gov/nchs/ppt/icd9/att_mucositis_sep05.ppt

symptoms (such as soreness), and functional disturbances (such as inability to eat). This scale is often used to describe the different stages of oral mucositis. The WHO scale is widely regarded as the gold standard despite the fact that the instrument was never tested for its reliability. Indeed there are many other tools described in the literature. The severity of oral mucositis is graded from 0, no mucositis, to 4[17] and grade 1 and 2 of the WHO can be compared with the upregulation and message generation phases while WHO grade 3 and 4 signal the ulceration phase.

To assess the development and severity of oral mucositis nurses need a valid and reliable assessment tool which is easy to interpret and with clearly understood parameters, an instrument that is comfortable for the patient and feasible in practice. Assessment should include thorough examination of the oral cavity, including lips, tongue, oral mucosa, gingival and palate evaluating the presence of erythema, oedema and lesions. Pain is one of the most distressing symptoms experienced by patients hence the use of a pain scale is an essential element of oral mucositis assessment.
However, insight into the validity and reliability of the large number of instruments available in the literature is incomplete and assessment tools are often not used in nursing care thus undermining the quality of assessment and preventive care[18].

Management

Systematic provision of oral care is probably more effective than any specific agents or devices in ameliorating the distress caused by oral complications. A vast number of agents have been studied for their potential usefulness in the prevention and treatment of mucositis, but none is highly effective. A 2006 Cochrane review of 29 interventions for the prevention of cancer treatment-related mucositis indicated some evidence of benefit for 8 agents including amifostine, antibiotic pastillea or paste, benzydamine, hydrolytic enzymes, vitamin E, cryotherapy, povidone iodine and, last but by no means least, oral care[19]. However most interventions involved medicines which require prescription and only few, specifically oral care, cryotherapy and several mouthwashes, can be incorporated into daily nursing practice.
Frequency, consistency, and quality are important factors in oral care [20-24]. Yet, published reports on the use and efficacy of oral care guidelines and protocols do not offer detailed guidance because the agents used and the frequency of administration vary widely and evidence for recommendations is often not provided. Assessment and criteria used to measure efficacy of oral care have been inconsistent. There is a lack of evidence for the current care given by nurses not only in terms of effective assessment, but also with respect to prevention and non-pharmacological treatments. Despite of the availability of various guidelines and systematic reviews, their place in practice is limited and their quality remains to be determined.
Moreover it is not clear which care nurses actually provide to patients at risk for oral mucositis nor which knowledge and skills they have in relation to the available evidence.

Finally, only a few studies have investigated what nurses actually know about oral care and none were found that reported practice improvement projects or whether knowledge and skills improve with oral care education sessions. In other areas such as pain management for patients with cancer, educational programmes designed to update knowledge in order to change pain management practices and patient outcomes were offered to nurses and were effective[25].

Aim of the thesis

The aim of this thesis was to make an inventory of, and to evaluate, different aspects of current nursing practice in the management of oral mucositis.
More specifically, we aimed to:

- describe current nursing practice and practice improvement in relation to oral mucositis directed care in haematology nursing
- evaluate available evidence for preventive care and treatment of oral mucositis and to evaluate guidelines in general oncology care.

The outline of the thesis

Part 1
Chapters 2 to 5 describe current nursing practice and practice improvement in haematology nursing.
A survey was undertaken of European transplant centres to gain a better insight into current nursing practice for the management of oral mucositis. The responses of 46 haematopoietic stem cell transplantation centres in 16 countries to this survey are reported in Chapter 2. To observe signs and symptoms of oral mucositis nurses need a valid, reliable and use-friendly assessment instrument. In Chapter 3 a systematic review was undertaken to summarize the scoring instruments that were available in the literature, and the development of a new instrument Oral Mucositis Nursing Instrument (OMNI)* was undertaken. To test the reliability of the OMNI, pairs of experienced nurses assessed the oral cavity of patients. The usability of the instrument was evaluated with a questionnaire. Chapter 4 investigated the responsiveness of the OMNI using the Guyatt's Responsiveness Index and the Receiver Operating Characteristic.
Chapter 5 investigated whether knowledge and skills about oral care improve when education is provided for nurses in charge of patients who are at risk for oral mucositis. This intervention study consisted of a baseline test on the knowledge and skills of nurses in the haematology wards of two different hospitals. Oral care education sessions were given in one hospital and follow-up tests were performed in both hospitals.

* *The OMNI was originally christened the Nijmegen Nursing Mucositis Scoring System, (NNMSS). For purpose of readability, we used ONMI throughout the text of this manuscript.*

Part 2

To investigate evidence and guidelines of oral mucositis in general oncology care several studies were carried out.

A number of reliable instruments are available to assess oral mucositis, but none is universally acceptable. A collaboration of multi-disciplinary experts from Europe was formed to formulate recommendations on oral mucositis assessment, based on a systematic literature review and expert experience. The results are presented in Chapter 6.

Chapter 7 describes a systematic review of the effectiveness of mouthwashes for the prevention of chemotherapy-induced oral mucositis and reports a meta-analysis on the effectiveness of chlorhexidine.

To investigate the evidence for oral mucositis nursing care, the quality of guidelines and systematic reviews for the prevention and treatment of oral mucositis was assessed, and reported in Chapter 8. The Appraisal of Guidelines for Research and Education (AGREE) instrument was used to assess the quality of the guidelines and the Overview Quality Assessment Questionnaire (OQAQ) was used for the quality of systematic reviews. The appendix presents the development and testing of the national guideline "Oral Mucositis of Patients with Cancer".

Finally, in Chapter 9, the main findings, strengths and limitations of this thesis are summarised and recommendations for future research are given.

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Chapter 2

Management of oral mucositis at European transplantation centres

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Abstract

Oral mucositis (OM), which occurs in many patients with hematologic malignancies treated with high-dose therapy and stem cell transplantation, is associated with substantial clinical, economic, and quality-of-life (QOL) consequences. It has been associated with an increased need for total parenteral nutrition and opioid analgesics, prolonged hospital stays, and increased risk of infection. The research subgroup of the European for Blood and Marrow Transplantation Nurses Group surveyed nurses at transplantation centres for their thoughts about the clinical, QOL, and economic consequences of OM; tools for assessing OM; strategies for preventing and treating OM; and the need for the development and implementation of treatment guidelines. The responses from 46 centres, in 16 countries, indicated that most nurses (91%) believe OM has a large effect on patients' QOL. Nurses are not highly satisfied with current treatments for OM, but they believe the discomfort is reduced with oral care protocols and mouthwashes. Oral mucositis is routinely and frequently assessed, however there are inconsistencies in how it is managed. Most centres used unpublished, centre-specific guidelines, and the survey found that most nurses agreed that published national guidelines would be valuable for standardising the assessment and management of OM.

Introduction

Oral mucositis (OM) is a major focus of nursing care in bone marrow transplantation (BMT) centres. Its incidence varies, depending on the chemotherapy regimen and the treatment modality, but it is especially common and severe in patients who undergo haematopoietic stem cell transplantation (HSCT), because of the high-dose, myeloablative chemotherapy used for conditioning. The rate of severe OM (grade 3 or 4) exceeds 60% in most reports on patients who receive total body irradiation, and it is 30% to 50% even without total body irradiation[1]. Early data from the Prospective Oral Mucositis Audit indicate that OM requiring treatment (grades 2-4) occurs in more than 60% of patients with haematologic malignancies who undergo HSCT[2].

Oral mucositis can range in severity from soreness and erythema to severe ulceration, which penetrates to the submucosal lining. Healthcare professionals tend to focus on the strict clinical definition of OM, which refers to erythema and ulceration; however, patients tend to express most concern about symptoms such as pain and xerostomia, and other oral cavity changes[3]. In a series of interviews of 38 patients with haematological malignancies who underwent BMT, 79% reported oropharyngeal changes, most frequently oral pain, sores, tender or sensitive mouth, and thick mucus[4]. Among all study participants, 42% rated OM as the single most debilitating complication of their transplant, far ahead of the second most troublesome complication, nausea or vomiting.

Because it disrupts the function and integrity of the oral cavity, OM can substantially decrease quality of life (QOL) and may also increase morbidity[5]. OM can be associated with severe pain, which can lead to cachexia, anorexia, dehydration, and severe malnutrition. It is estimated that a large proportion of adults undergoing haematopoietic stem cell transplantation (HSCT) require feeding tubes and narcotic analgesics[5]. Severe OM causes impairment in functional activities such as eating, swallowing, and talking, which affect social interactions and emotional well-being[6, 7]. In addition, patients have attributed increased depression and sleep disturbances to OM[8]. Oral mucositis may also affect the risk of death in the transplant setting. In the first multicentre study to consider the impact of OM, Sonis et al. analyzed data on 92 patients undergoing BMT and found that each 1-point increase in OM severity on the Oral Mucositis Assessment Scale was associated with a nearly 4-fold increase in 100-day mortality[9]. More recently, Fanning et al. showed that in patients who underwent autologous HSCT for haematological malignancies, severe mucositis was a significant risk factor for all-cause mortality and relapse mortality[10].

The multicentre study by Sonis et al. also showed that increasingly severe OM was associated with progressively worse morbidity and economic outcomes. Each 1-point in crease in OM severity on the Oral Mucositis Assessment Scale was associated with a 2-fold increase in the risk of significant infection, 3 additional days of total parenteral nutrition, 3 additional days of injectable narcotic analgesia, and 3 additional days in the hospital resulting in additional hospital charges[9]. There was a statistically significant association between the severity of OM and each of these outcomes. The mean hospital charge was higher among patients with ulceration than among those without OM ($P = 0.06$).

Patients treated with myelosuppressive chemotherapy are already at increased risk of infection due to neutropenia, and breakdown of the mucosal barrier due to OM exacerbates the incidence of bacteraemia and sepsis[5, 11]. For these and other reasons, OM is increasingly being recognised as a major dose-limiting toxicity. It can disrupt cancer treatment by requiring breaks in radiation therapy, reductions or delays in chemotherapy, modifications in the selection of chemotherapeutic agents, or discontinuation of optimal cancer therapy[5, 12].

Nurses are in a prime position to perform the day-to-day assessment of OM, and as such are integral to its management; moreover, they are the primary source of information for patients concerning treatment options. In an effort to understand practice patterns across Europe, in 2004 we surveyed nurses at European BMT centres to learn more about how they prevent and treat OM. This paper presents the results of the survey and their implications for improving nursing care of OM in the transplant setting.

Materials and methods

The research subgroup of the European for Blood and Marrow Transplantation Nurses Group (EBMT-NG) used a questionnaire to assess nurses' impressions of the management of OM in adult patients with haematological malignancies who are undergoing either autologous or allogeneic bone marrow or peripheral stem cell transplant. This questionnaire was developed by adapting a survey of practices in oral care in children who are treated for cancer[13]. The questionnaire, which was distributed in October 2004, addressed:

- Nurses' impressions of the QOL, clinical, and economic consequences of OM
- Tools for assessing OM
- Strategies for preventing and treating OM
- Need to implement and use guidelines for OM

Nurses at 100 European BMT centres were invited to participate. These centres were selected because they performed the most stem cell transplantations in 2004 and were members of EBMT. The research sub-group of the EBMT-NG encouraged participation and followed up with any nonresponders.

Results

There were responses from nurses from 46 centres in 16 countries: Italy (9), United Kingdom (6), Germany (5), Spain (5), Belgium (3), Sweden (3), Switzerland (3), Czech Republic (2), the Netherlands (2), Poland (2), Austria (1), Denmark (1), Finland (1), France (1), Ireland (1), and Slovenia (1). Most of the nurses (74%) surveyed had between 6 and 15 years experience in caring for BMT recipients.

Nurses' impressions of QOL, clinical, and economic consequences of OM

Most nurses believed that OM affects the length of time that patients are unable to perform daily activities such as eating, drinking, talking, and receiving visitors (Figure 1). A majority (91%) also believed that OM has a major negative effect on patients' QOL (Figure 2).

Figure 1: *Nurses' perceptions of the mean length of time patients were unable to perform everyday activities because of oral mucositis.*

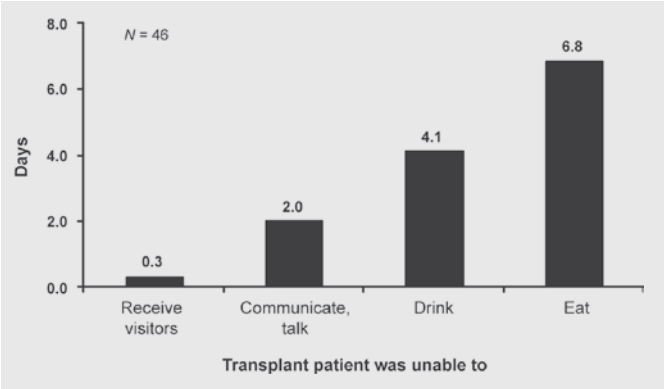
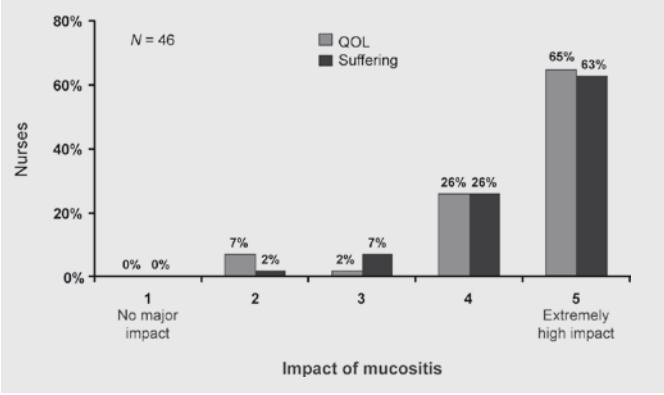
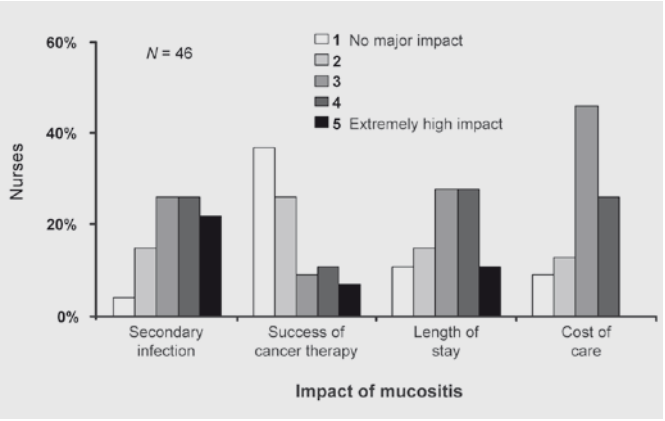


Figure 2: *Nurses' perceptions of the effects of oral mucositis on patients' quality of life (QOL).*



Most respondents did not believe that OM influences the success of cancer therapy but did believe that it has clinically significant effects on the risk of secondary infections, the length of hospitalisations, and the costs of care (Figure 3).

Figure 3: *Nurses' perceptions of the effects of oral mucositis on patients' clinical and economic outcomes.*



Assessment of OM by nurses and centres

Most nurses reported that they assess for OM routinely and often at their centres; 91% of centres assessed patients at least once a day, with 31% assessing them 3 or more times a day. Eighty-four percent of centres began their assessments at the start of treatment, regardless of the condition of the patient's mouth, and the others assessed patients only after OM had developed or they had had difficulty in swallowing or eating. Most nurses (70%) reported that they do not increase the frequency of assessments in patients with an increase in the severity of OM, possibly because the additional assessments might add to the patient's pain.

Fifty-nine percent of nurses used standardised scales for assessing OM. The most commonly used scales are the World Health Organization Oral Mucositis scale, the Oral Mucositis Assessment Scale, and the Oral Assessment Guide [14-16]. Of the nurses surveyed for this study, 74% used the World Health Organization Oral Mucositis scale, 4% used the Oral Mucositis Assessment Scale, and another 4% used the Oral Assessment Guide. Almost all nurses agreed that the grade of OM has an effect on the initiation of both parenteral nutrition (94%) and narcotic analgesics (98%).

Inconsistent treatment across centres

Preventive care was routinely used in more than 90% of all patients who underwent either allogeneic or autologous BMT, however, there was substantial variation on the treatment of OM between centres. Only 70% of centres routinely implemented treatment for all patients with grade 4 OM, while 9% of centres reported that patients with grade 4 OM were not treated at all (Table 1). A modest number of centres (33%) reported that they used early intervention and routine treatment at the first sign of oral ulcers in all patients with less severe OM.

Table 1.: *Treatment of oral mucositis (not including prevention measures) across centres by severity of oral mucositis*

	Centres that treat (%)		
Patients treated for OM	WHO grade 1 or 2	WHO grade 3	WHO grade 4
100%	33	54	70
80%–99%	4	2	—
60%–79%	2	13	—
40%–59%	11	4	—
20%–69%	9	2	4
1%–19%	7	4	7
0%	24	9	9
No response	11	11	11

Strategies for managing OM

In the absence of effective measures for preventing OM at the time of this survey, oral hygiene methods were recommended to 87% of patients who underwent transplantation; dental gels, antimicrobial rinses, and antibiotics were also frequently used. Methods for preventing and treating OM are shown in Table 2. Nurses identified that treating OM differed from preventing it, mainly with respect to the use of more frequent rinsing, as well as greater use of narcotic analgesics and other pain management methods. Sixty-nine percent of nurses believed that controlling pain was an adequate means of treating OM, and 96% reported that they used narcotic or other analgesics for treating the pain. The duration of treatment with narcotic analgesics that was reported varied by the severity of the OM, with mild OM (grade 1) and moderate OM (grade 2) being treated for a mean of 2.4 days, grade 3 for 6.5 days, and grade 4 for 9.5 days.

Fewer than half of the nurses surveyed were aware of newer treatment options for OM. Keratinocyte growth factor was the best known, with 44% of nurses having heard of it, even though at the time of the survey it was only available in clinical trials. A third of nurses were familiar with Gelclair, a bioadherent gel, and L-glutamine, with 2% aware of the use of vitamin E in the management of OM.

Table 2.: *Strategies for managing oral mucositis*

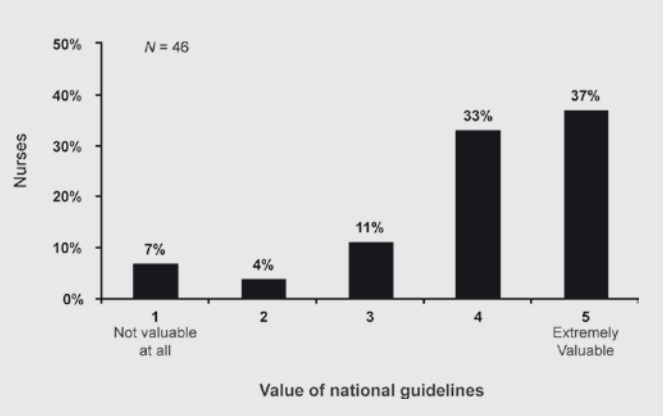
	Nurses using strategy (%)		
Strategy	For prevention	For treatment	Mean satisfaction score[1]
Oral hygiene	96	96	4.1
Chlorhexidine	61	65	3.1
Rinses-antimicrobial	46	63	3.1
Antibiotics	41	50	3.3
Rinses-bland	30	43	3.4
Ice chips	22	35	3.3
Granulocyte or granulocyte-macrophage colony-stimulating factor	13	26	2.5
Sucralfate	9	22	3.1
Benzydamine	7	17	2.1
Prednisone	7	15	3.6

[1]Satisfaction was rated on a scale of 1 to 5, with 1 being "not satisfied at all" and 5 being "extremely satisfied." The mean score reflects the nurses' satisfaction with both the prevention strategies and the treatment strategies.

Guidelines for assessing, preventing, and managing OM

Most of the nurses (78%) surveyed thought that they, not physicians, have primary responsibility for implementing centre-specific guidelines. More than two thirds of the nurses agreed that national guidelines would be valuable in managing OM at their centre (Figure 4).

Figure 4: *Nurses' perceptions of the value of national guidelines for managing oral mucositis.*



The key benefits cited included; standardisation of care (18%), implementation of evidence-based guidelines in their practice (11%), and potential for common standards for comparative trials (7%). Eighty-eight percent of the nurses and centres routinely and consistently used guidelines or protocols for oral care; of these, 90% (78% overall) used centre-specific guidelines for managing OM and 15% used published guidelines. The survey questionnaire did not address whether the centre specific guidelines were adapted from or incorporated parts of the published guidelines. The 13% of nurses and centres that did not consistently use guidelines cited one or more of the following reasons: little staff awareness of the existing guidelines (50%), current guidelines are outdated (50%), and current guidelines are impractical (25%).

Discussion and conclusions

Oral mucositis is a painful and debilitating complication in many patients treated with myeloablative conditioning therapy and BMT, and it can have serious clinical, economic, and QOL consequences. To gather information about current practice across Europe, we surveyed nurses about their perceptions of oral care at European BMT centres. The nurses agreed that OM has major effects on the QOL and the costs of care of patients who undergo BMT. The survey also found inconsistencies in the treatment of OM across centres and the need for a more standardised approach. Not all centres treated patients with grade 4 OM, a debilitating condition, while in contrast some centres used early intervention and initiated treatment at the first appearance of oral ulcers.

These findings confirm observations by McGuire et al. about the need for a consistent and unified approach to performing OM assessments and the need for updated guidelines for assessment and treatment[17]. The survey respondents agreed that national evidence-based guidelines can help standardise the assessment, prevention, and treatment of OM in European BMT centres. In 2004, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology published evidence-based guidelines for preventing and treating chemotherapy-induced OM, which were based on a review by 36 panellists of the literature published between 1996 and 2002 [1]. In the absence of effective strategies for preventing and treating OM, the guidelines recommended oral hygiene as the preferred strategy for managing the condition. The 2005 update of the guidelines now recommend the use of palifermin (Kepivance®, recombinant human keratinocyte growth factor-1) in patients with haematological malignancies who receive myeloablative therapy and HSCT[18]. Our survey found that fewer than half of the nurses who responded were aware of palifermin or other newer therapies for OM. It is important that nurses educate themselves about the guidelines and keep up with novel therapies, innovative mechanisms of action, new concepts about pathobiology, and future trends in the management of OM.

It should be noted that this article is based on nurses' perceptions of the management of OM in European transplant centres. There are several limitations to this approach. The results of this study may not be generalisable since the sample was small. The potential bias in responses should also be considered because of the response rate of 46%. It is also possible that the respondents may not have answered questions accurately or honestly, even though confidentiality was assured. Further, reports were not independently verified, although this may not be important because the study focused on the nurses' perceptions. Despite these limitations, we believe that these results provide useful insight into the management of OM in European transplant centres.

Most nurses surveyed believe that OM is a debilitating condition in patients who undergo transplantation and that European BMT centres lack uniform methods and protocols for assessing, preventing, and treating it. Once uniform evidence-based national guidelines are established, they can be implemented into clinical practice, followed by continuous quality improvement programs to evaluate changes in practice patterns and potential improvements in outcomes. The expert oral mucositis assessment group, made up of nurses, physicians, and dentists from EBMT and the European Oncology Nursing Society, is currently working to prepare guidelines to support the practice of oral assessment. Greater awareness of potential new therapies for OM can be expected to help nurses improve the QOL of their patients who have OM.

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Chapter 3

A scoring system for the assessment of oral mucositis in daily nursing practice

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Abstract

Nurses take care of patients around the clock, so they are in an ideal position to observe and record the signs and symptoms of oral mucositis. This requires a valid, reliable scoring instrument that is easy to use. The objectives of this study were to summarize the scoring instruments that are available, to develop a new Oral Mucositis Nursing Instrument (OMNI) and to evaluate this new instrument. A systematic review was undertaken in which 21 scoring instruments were reviewed and compared. None of the instruments studied satisfied the criteria that were established beforehand. The six most common items from the systematic review were selected for the new instrument. To test the OMNI, pairs of experienced nurses assessed the oral cavity of 26 patients independently. Inter-observer reliability (Kappa), correlation between items (Spearman's rank–order correlations) and internal consistency of the instrument (Cronbach's alpha) were calculated. The usability was evaluated with a questionnaire. Cohen's weighted Kappa was within an acceptable range. Almost all correlations were statistically significant and in the predicted direction. The Cronbach's alpha coefficient indicated sufficient internal consistency. All nurses found the OMNI user-friendly and suitable for day-to-day care. The OMNI can be used as a valid, reliable and usable instrument in daily nursing practice.

Introduction

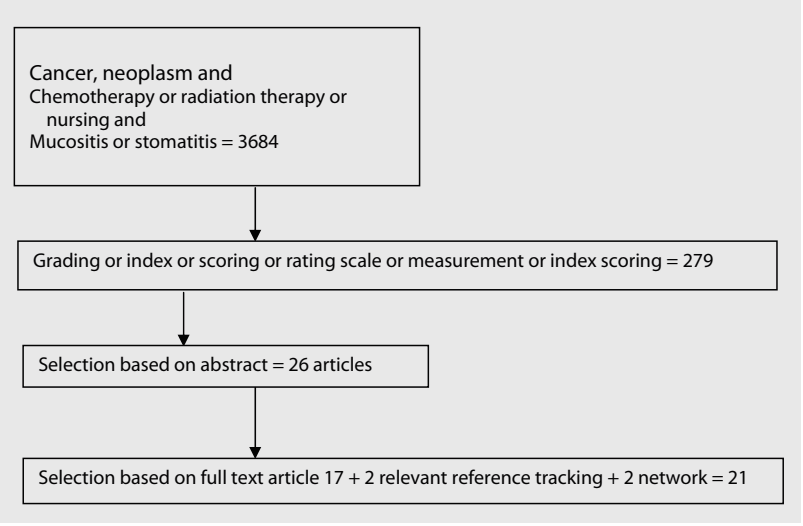
Mucositis is an important and frequent complication of patients after treatment with cytostatic chemotherapy. Up to 40% of patients are affected by oral mucositis following cytostatic chemotherapy[1], as are almost all those who have undergone a haematopoietic stem cell transplant (HSCT), with 67% developing severe oral mucositis[2].
Oral pain associated with oral mucositis is the most common complaint reported by patients[3], and results in difficulties in chewing, swallowing and speaking[4]. Other symptoms include inflammation, oedema and lesions in the mouth. There is also a serious risk of infection which can lead to fulminant sepsis of patients with reduced immunity[4-6].
It is essential that mucositis is recognized at an early stage, so that adequate measures can be taken and the results of these interventions can be evaluated.
One of the tasks of nurses is to observe changes in the patients' condition, including those involving the oral mucous membranes. Scoring mucositis is therefore within the remit of nurses.
A valid and reliable instrument for evaluating oral mucous membranes is essential, and a number of scoring instruments have been described. However, these instruments were developed for various purposes. For example, instruments have been developed from the perspective of dentistry e.g Hickey et al.[7], radiotherapy e.g. Lievens et al.[8], oncology e.g. World Health Organization[9] and nursing e.g. Eilers et al.[10]. Most of these instruments were designed to evaluate the effects of a particular intervention. Others have been specifically designed to measure oral mucositis and monitor its progress, including one developed in our own department Donnelly et al.[11]. Inter-rater reliability of the instruments was not important as they were frequently used by a few researchers. However, this may make them less suitable for a daily nursing practice, which requires a reliable validated instrument that is robust enough to remain reproducible despite the steady change over of staff with each shift. The instrument also has to be usable in daily nursing practice employing items that are clearly described, requiring the fewest possible number of aids and affording assessment that is as comfortable as possible for the patients and convenient for the nurses.
The current study had three objectives: first to perform a literature review to summarize the scoring systems available, second to select an instrument comprising those items best suited to daily nursing practice and third, to evaluate the validity, reliability and usability of this instrument.

Methods

Systematic review
A systematic literature review was undertaken to find a validated, reliable and a useful scoring instrument for daily nursing practice.
To identify relevant scoring instruments, the databases Medline and Cinahl were searched for literature up to June 2004, with the keywords neoplasm, cancer, radiation

therapy, chemotherapy, nursing, mucositis, stomatitis in combination with grading system, rating scale, measurement, index scoring. Articles were included in this study if the scoring instrument was completely described. A total of 17 instruments were found. In addition, two instruments were found using references of relevant articles. Finally, two instruments (graduation papers) were found via the network. This resulted in a total of 21 widely varied instruments (see Figure 1). Data were collected for all instruments concerning domains of oral mucositis, reliability, validity and the usability.

Figure 1: *Selection of articles*



Development of the instrument

Based on the systematic literature review of scoring instruments, a new scoring instrument for daily nursing practice was developed. The development began with a selection of descriptive items to encompass the range of changes in the oral cavity classically appearing in patients treated with cytostatic chemotherapy. The six most prevalent items of 21 scoring instruments are used for the composition of the new instrument. This new instrument was then presented to a panel of experts (nurses and physicians) for their comment. Finally, the instrument was then tested in daily nursing practice.

Evaluation of the instrument

The OMNI was tested in February and March of 2004 in the haematology ward of the Radboud University Nijmegen Medical Centre in the Netherlands. The haematology ward has 28 patient beds admitting patients for cytotoxic chemotherapy, and autologous and allogeneic HSCT.

Patients participating in this study had to be ≥ 16 years of age, able to read and comprehend Dutch, and estimated to be hospitalized for 21 days. Patients were nursed in rooms supplied with air under positive pressure. All patients participating in the stu-

dy received a standardized oral care protocol, consisting of four times a day rinsing and brushing the oral cavity, to use a soft toothbrush and toothpaste of choice and to renew the toothbrush every week and if necessary, to moisturize lips with Vaseline. Twenty-six successive either allogeneic or autologous HSCT recipients were included in this study.
Eight certified nurses with experience in haematology care participated in this study.
Each patient was examined by two nurses; within ½ hour the nurses assessed patient cavity independently. The assessment took place in a systematic manner, a penlight and a spatula was used for good inspection.
After examining the patient's oral cavity, nurses had to fill out the form of the OMNI.

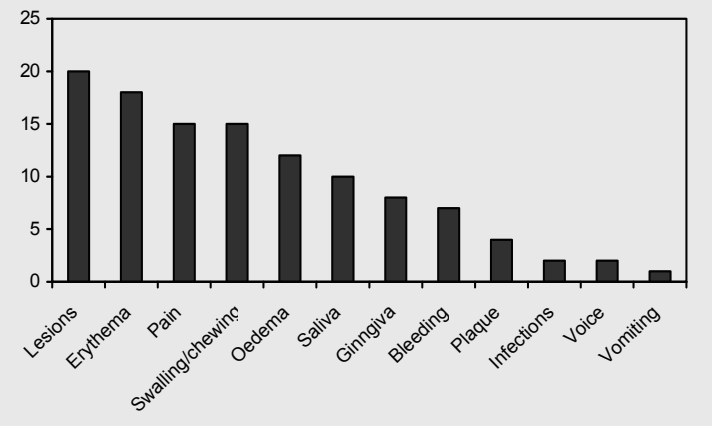
Analysis procedures
The internal consistency of an instrument is the degree to which the items of an instrument are all measuring the same attribute or dimension. Cronbach's alpha was computed for the new instrument and Spearman's rank–order correlations were calculated for all items. The reliability evaluation furthermore included the inter-observer reliability. Cohen's weighted Kappa[12] was calculated for all observations.
The usability of OMNI was evaluated with a questionnaire for the nurses involved.

Results

Systematic review
The origin and purpose of the instruments largely determine their structure and contents. There were four instruments originating from oncology, two from radiotherapy, seven each from dentistry and nursing, and one instrument was designed in a multidisciplinary setting.
Roughly speaking, two stereotypical scoring instruments emerged from the literature: ordinal and numeric instruments. Ordinal instruments classify the symptoms into previously described categories, where the severity of the mucositis is determined and graded. An example of these instruments is the World Health Organization[9] grading scale. The categories are broad and subject to interpretation: thus, the WHO instrument is not useful for assessing small changes over time.
Numerical instruments are those where the severity of the symptoms is measured and where a numerical system defines the status of the mucositis; this may or may not be followed by classification into categories. Examples of these instruments are the Oral Assessment Guide (OAG) developed by Eilers[10] and the Oral Mucositis Assessment Scale (OMAS) developed for testing the effects of intervention[13], and the Daily Mucositis Score (DMS) developed in our own department to monitor the progress of mucositis in relation to infectious complications[11]. Most of the instruments based their validation on the result of consensus statements from cooperative groups or a small number of experts in the field. Only nine scoring systems of the 21 found in the literature evaluated the reliability of the instrument under study.

Objective changes (erythema, lesions, oedema), subjective changes (pain or sensitivity, dryness) and functional changes (voice, swallowing, chewing) are all used in the various instruments. Figure 2 shows the most prevalent items and/or symptoms of 21 scoring instruments. Obviously, the origin of the instrument plays a role in the selection of the items.

Figure 2: *Most prevalent items/symptoms of 21 scoring instruments*



For example, gums and teeth are items that play a role especially with instruments that have their origin in dentistry. Seven instruments have their origin in nursing (see Table 1). Only one instrument, the Western Consortium for Cancer Nursing Research

Table 1: *Overview of the nursing scorings instruments*

	Validity	Reliability	Usability	Scale	Items/symptoms
WCCRN [14]	Expert, construct	No	No	3 stages	Per stage extended description of the oral cavity
OAG [10]	Expert, content	Inter-Observer range 70% - 100%	No	3 point	8
OCAF [15]	Yes (adaptation OAG)	No still on research*	No	4 total=severity mucositis	5 items in 13 locations in the oral cavity
McDibbs [16]	Expert	Inter- Observer: 13 items 100% lesions 85%	No	7 items. 3 point 1 item score in mm and 3 item present-/absent	11 items
OMI-20 [17]	Construct	Test-retest: range 0.38-0.86 p=0.001 Inter-Observer: range 0.80 - ≥0.90	No	4	2 in 9 locations in the oral cavity 1 location 1 in the oral cavity 1 location 1 in the oral cavity
Nieweg[18]	Expert	Inter-Observer: 63% - 53%	No	3 point for each item differ value	12
MSS[19]	Expert	Inter-Observer: Kappa range 0.62-0.96	No	4	6 from which 3 in 7 locations in the oral cavity

* No later publication could be found that showed the reliability
OAG: Oral Assessment Guide; OCAF: Oral Cavity Assessment Form; OMI:Oral Mucositis Index;
WCCNR: Western Consortium for Cancer Nursing Research stomatitis staging system

(WCCNR) stomatitis staging system [14] is compound in a ordinal scale. It consists of three stages of extended descriptions of the oral cavity. For daily nursing practice, this is impractical, because it requires nurses to memorize the three stages in order to classify patients' cavity into a stage. Six nursing scoring instruments use a numeric structure.
The number of items or symptoms varies from four Oral Mucositis Index (OMI)-20[17] to 12 Nieweg[18]. The OAG[10] is the only instrument that does not measure pain as a symptom of oral mucositis[20]. Oral pain rise and fall predictably during the course of oral mucositis. Three nursing scoring instruments[15, 17, 19] are complicated in the assessment of the oral cavity. They require the assessment of several items or symptoms on specific locations in the oral cavity, and items or symptoms vary per location. This requires nurses to memorize all aspects of the complete instrument during the assessment of the oral cavity and for patients with severe pain to open their mouth for sufficient time.
In a number of instruments, different tools are necessary to correctly inspect the oral cavity. A penlight or a spatula are practical tools for mouth inspections, but a periodontal probe[16] to measure the length of a lesion is too complicated for daily nursing practice and requires a significant amount of training. Some of the instruments require arithmetic methods to calculate the total scores. Sometimes, different items must be multiplied with definite values or mathematical formulae to score the patient's oral cavity into a category or grade[18]. This procedure is susceptible to miscalculations. In general, the ordinal scales require the stages to be memorized in order to classify patients cavity. As these stages are defined using complex combinations of symptoms, mistakes in classifying can easily occur. Therefore, numerical instruments appear to be better suited for daily nursing practice, as they require the evaluation of one symptom at a time. If measurements take place on a daily basis, the total scores provide an overview of the progression of the mucositis.
None of the instruments studied satisfied the criteria that were established beforehand: valid, reliable and usable in daily nursing practice.

Development of the Oral Mucositis Nursing Instrument (OMNI)
The systematic literature review of scoring instruments showed that the most prevalent items (see Figure 1) used in the various scoring instruments were erythema, oedema, lesions, pain and saliva production, which is mostly expressed by dryness of the mouth and saliva viscosity.
These six items were added together to generate a mucositis score, which was used to monitor the development, progression and course of mucositis on a daily basis (see Table 2). A 4-point scale was used for four items – oedema, lesions, pain and dryness of the mouth and, a 3- point scale for two items – erythema and saliva viscosity. For each item, a score of 0 was assigned to the normal or desirable condition. The degree of oral pain was gauged with the help of a visual analogue scale (VAS), a 10-mm line with 0 indicating no pain and 10 representing the worst possible pain. Patients were required to indicate the dryness of their mouth into normal, mild, moderate and severe, scored as 0, 1, 2 or 3. The viscosity of the saliva is required to be scored as normal, slimy or viscous with a score of 0, 1 or 2.

The overall oral assessment score is the sum of the six scores.
The scoring system was then presented to a panel of five experts (nurses and physicians) in the area of oral problems of oncology patients. The panel did not recommend any major change.

Table 2: *Oral Mucositis Nursing Instrument*

Objective characteristics of oral mucositis (Mouth inspection by the nurse)				
	0 point	*1 point*	*2 points*	*3 points*
Erythema	Pink and moist	Mild/moderate	Severe	
Oedema	Absent	Mild -Print of teeth in tongue edge -Gingival swollen and red	Moderate -Print of teeth in tongue -Gingival swollen and white	Severe -Swollen tongue -Gingival swollen and shining white
Lesions	Absent	1 to 4	> 4	Elapse ulceration
Subjective characterises of oral mucositis (Information from the patient)				
	0 point	*1 point*	*2 points*	*3 points*
Pain	None	VAS score < 3	VAS score 4,5,6,	VAS score >6
Dryness mouth	Normal	Mild	Moderate	Severe
Viscosity saliva	Normal	Slimy	Thick	

VAS, visual analogue scale

Testing the Oral Mucositis Nursing Instrument (OMNI)
According to the newly devolved instrument, nurses were instructed to examine patient's oral cavity in a systematic manner. The lips, tongue and oral mucosa of the gingival, palate, uvula and tonsillar crypts were evaluated for the presence of erythema, oedema and lesions, and patients were required to indicate the degree of oral pain using the VAS and to indicate the dryness of their mouth and the viscosity of the saliva.
There were 15 male and 11 female patients aged 16– 70 years, with a mean age of 47 years. All had been admitted for an HSCT, 14 received an allogeneic HSCT and 12 an autologous HSCT. Eleven of the patients had acute myelogenous leukaemia (AML), eight had acute lymphocytic leukaemia (ALL), four Non-Hodgkin's lymphoma and three patients had multiple myeloma (MM). All patients admitted to the haematology ward were eligible to this study.
Individual mucositis scores ranged from 0 to 13, with 50% of the patients having a total mucositis score <4, 15.4% of the patients having a score 5–8, only 3.8% of the patient having a total mucositis score 9–12 and 7.7% of the patients score>13. Eight nurses participated (four men and four women), all of whom were graduates and six had spe-

Table 3: *Spearman's rank-order correlations (n=26)*

	Erythema	**Oedema**	**Lesions**	**Pain**	**Dryness**	**Viscosity**	**Total score**
Erythema	1.000	.364**	.520**	.255*	.475**	.137	.704**
Oedema		1.000	.389**	.262*	.183	.195	.612**
Lesions			1.000	.330**	.405**	.177	.653**
Pain				1.000	.266*	.215	.595**
Dryness					1.000	.052	.680**
Viscosity						1.000	.435**
Total score							1.000

* Correlation is significant at the 0.01 level (1-tailed).
** Correlation is significant at the 0.05 level (1-tailed).

cialized training in oncology. They had worked in the haematology for 1–5 years, and were familiar with daily mouth inspection.

Spearman's rank–order correlations were calculated between all items and the total scores of the OMNI (Table 3). Almost all correlations were statistically significant and in the predicted direction. Only viscosity of the saliva correlated negatively with the total instrument.

The internal consistency using Cronbach's alpha coefficient for the OMNI was 0.729, indicating modest, but sufficient internal consistency. Deletion of viscosity improved the instrument (Table 4).

Table 4: *Item-Total Statistics (n=26)*

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
Erythema	3.85	9.544	.642	.656
Oedema	3.46	9.351	.454	.695
Lesions	4.00	7.882	.690	.615
Pain	4.04	9.097	.455	.695
Dryness	3.56	8.879	.437	.704
Viscosity	4.17	11.597	.157	.760

The inter-observer reliability was assessed by comparing the measurements of pairs of nurses (Table 5). The reliability is considered very good for values >80, good for values 61–80, and moderate for values 41–60.

With exception of oedema, the Cohen's weighted Kappa of all the items of the new instrument was in the acceptable range.

The examination of the patient's oral cavity took 2–5 min, and all nurses found the OMNI use-friendly. Erythema and oedema were the most difficult to assess, according to 63% and 72% of the nurses respectively.

Table 5: *Inter-observer reliability for nurses (n=8)*

Items	Inter-observer κ
Erythema	0.60
Oedema	0.26
Lesions	0.73
Pain	0.83
Dryness	0.78
Viscosity	0.72

Discussion

This study describes the development and testing of a new instrument. The OMNI was developed as a result of the need to find an instrument that accurately assesses the patient's oral cavity in daily nursing practice. Validity of the OMNI, based on the systematic review, appears to be strong, and the internal consistency analysis indicates good internal consistency of the scale. Viscosity contributed little to the OMNI and was therefore deleted. The reliability of the OMNI was in acceptable ranges, although difficulties

were encountered with scoring erythema and oedema. In spite of what nurses reported concerning the symptom erythema, the Cohen's weighted Kappa coefficient shows opposite values. Probably, nurses feel uncertainty, but assess this symptom more accurate than they themselves expect. The weighted Cohen's Kappa coefficient for the symptom oedema underlined the nurses' expectations. Despite of the sufficient clinical experience nurses had, assessment of the symptom oedema should be trained and described in more detail to increase the reliability of the OMNI. The teaching and training of the nursing staff in the use of the OMNI is necessary to guarantee a reliable and correct assessment of the oral cavity.

The instrument was tested in a group of HSCT recipients. To enlarge the use and availability of the OMNI, it should also be tested in a group of patients who receive other cancer therapies. Another limitation of this study is the small sample size, a larger study will provide more information about the instrument and its use. The OMNI was tested for validity, reliability and usability; future studies need to involve the testing of responsiveness. Responsiveness refers to the extent that instruments are capable of differentiating among clinically relevant changes. In daily nursing practice, patient allocation is the most common operating procedure. Often, the same nurse cares for the same patient for a specific period of time. Therefore, it would be interesting to know the intraobserver reliability of the OMNI.

The importance of an instrument to assess oral mucositis is based on the premise that nurses should be able to identify chemotherapy-induced mucositis early, so that they can intervene to help minimize its severity and enable them to evaluate the effectiveness of oral mucositis treatment with various oral care protocols.

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Chapter 4

Establishing the responsiveness of the Oral Mucositis Nursing Instrument

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Submitted

Abstract

Oral mucositis is a burdensome and potentially dangerous side effect of chemotherapy and radiotherapy. Oral assessment is an important first step when identifying management strategies for oral mucositis. The Oral Mucositis Nursing Instrument (OMNI) is a valid, reliable and user-friendly instrument to assess oral mucositis in patients treated with chemotherapy and/or radiotherapy. However, to evaluate the results of nursing interventions an instrument should also be able to detect clinical relevant changes.
This study investigated the responsiveness of the OMNI.
The oral mucositis data came from a cohort of 32 recipients of a haematopoietic stem cell transplant unit who had participated in a prospective trial of parenteral glutamine. Evaluations of oral mucositis began between day 7 and 28 after conditioning. Responsiveness was investigated using two approaches: Guyatt's Responsiveness Index and the Receiver Operating Characteristic (ROC) curves.
Guyatt's responsiveness index for the OMNI instrument is 2.2, indicating good sensitivity for detecting changes in oral mucositis over time. The ability of the OMNI to detect day-to-day deterioration (or improvement) was further expressed by the areas under the two corresponding ROC curves of 0.89 and 0.92 respectively.
The adequate responsiveness of the OMNI suggests it is a good instrument for measuring oral mucositis on a daily basis.

Introduction

Oral mucositis is a common complication of chemotherapy and radiotherapy and can be a significant complication for patients undergoing cancer treatment or haematopoietic stem cell transplant (HSCT)[1].

It is essential that mucositis is recognised at an early stage so that adequate interventions can be taken and the results of these interventions can be evaluated. One of the tasks of nurses is to observe changes in the patient's condition including those involving the oral mucous membranes. A valid and reliable instrument for evaluating oral mucous membranes is essential. In the literature, a number of scoring instruments have been described. However, these instruments were developed for various purposes for example research into the relationship between bacteraemia and mucositis[2], day-to-day care[3] and from different perspectives for example dentistry [4], oncology [5] and nursing[3]. Most of these instruments were designed to evaluate the effects of a particular intervention. Others were designed to measure oral mucositis and monitor its progress. Roughly speaking, two typical scoring instruments emerged from the literature: ordinal and numeric instruments. Ordinal instruments classify the symptoms into predefined categories, where the severity of the mucositis is determined and graded. Numerical instruments are instruments where the severity of component signs and symptoms is assigned a score and the individual scores are summed together to produce an overall score that defines the degree of the mucositis; this may or may not be followed by classification into categories. The numerical instruments appear to be better suited for daily nursing practice. If measurements take place on a daily basis, the total scores provide an overview of the progression of the mucositis. Most of the instruments based their validation on consensus statements from co-operative groups or a small number of experts in the field. Objective changes (erythema, lesions, oedema), subjective changes (pain or sensitivity, dryness) and functional changes (voice, swallowing, chewing) are all used in the various instruments. Some instruments are complicated as they require the assessment of several items or symptoms at specific locations in the oral cavity and items or symptoms vary for each location. In a number of instruments, different tools are necessary to correctly inspect the oral cavity. Also, some of the instruments require arithmetic methods to calculate the total scores. This procedure is susceptible to miscalculations.

Given the problems outlined above, the Oral Mucositis Nursing Instrument (OMNI) was developed and validated. The quality of an instrument in general relates to three concepts: validity, reliability and usability. Responsiveness (or sensitivity to changes) is the ability to detect change over time[6]. Though seldom seen as a separate aspect of the quality of an instrument, since it could be argued that responsiveness relates to the validity of the instrument, a responsive instrument allows closer monitoring which may be important for deciding to intervene and also for determining when a response occurs.

The literature is unclear about what is an adequate approach for evaluating responsiveness[7]. According to Husted et al.[8] two major aspects of responsiveness can be described,

namely internal and external responsiveness. Internal responsiveness characterizes the ability of a measure to change over time when change would be expected. External responsiveness is the extent to which change in a measure relates to corresponding change in a reference measure of clinical health status. One method for assessing internal responsiveness is to evaluate change in a measure which has been assessed using a single group repeated measures design, where patients are assessed before and after a known treatment. In oral mucositis, responsiveness implies that the instrument should correlate with known patterns of mucositis progression. The changes in scores should then reflect this pattern.
The aim of the present study was to establish the responsiveness of the OMNI in a longitudinal study design.

Patients and Methods

The data for this assessment originated from a cohort of 32 patients of a haematopoietic stem cell transplant unit who had participated in a prospective randomised placebo-controlled study which failed to show any benefit of parenteral nutrition supplemented with glutamine-dipeptide on oral mucositis [9].
The patients who had participated were all adults of 18 years of age or older and had received the same myelablative conditioning therapy namely idarubicin at a dose of 42 mg/m^2 by continuous infusion over 48 h starting 12 days before transplant (SCT day −12), 120 mg/kg cyclophosphamide (60 mg/kg per day on SCT days −6 and −5) and 9 Gy of total body irradiation (4.5 Gy per day on SCT days−2 and −1)[10].
All were nursed in rooms supplied with air under positive pressure and had followed the same supportive care protocol which included prophylactic antimicrobial agents. Oral care consisted of rinsing and brushing the teeth four times a day using a soft toothbrush and the toothpaste of choice and renewing the toothbrush every week. The patients' lips were moisturised with Vaseline when necessary. Morphine was given on demand to control pain related to oral mucositis.

Mucositis assessment
Assessment of oral mucositis was performed daily by a trained nurse who inspected the mouth in a systematic manner with a penlight and a spatula.

OMNI
The Oral Mucositis Nursing Instrument (OMNI) was develop in a previous study that included a systematic review of the literature, expert validation and testing of its reliability and usability in a group of hematopoietic stem cell transplant (HSCT) patients. Six items commonly found in other oral mucositis assessment instruments were selected for the new instrument. These included erythema, oedema, lesions, pain, dryness of the mouth and salvia viscosity. The salvia viscosity item was deleted from the initial instrument after initial testing, as it contributed little to the scale.

Erythema, oedema and lesions are observed by nurses, while patients' self assessments are used for pain and dryness of the mouth. A three point scale is used for the erythema item, whereas four point scales are used with all other items. The four point scale for pain is a transformation of a visual analogue scale where patients are asked to select a number from a 0 to 10 range, 0 representing no pain and 10 representing the worst possible pain. As with pain, 0 represents a normal or most desirable condition for every OMNI item. The total oral assessment score from the instrument is calculated by adding the scores for each of the items (0-14 range).
From the previous study, the validity of the OMNI appeared to be strong, its reliability was acceptable and nurses found the instrument user friendly[11].

DMS
The Daily Mucositis Score (DMS)[2] was routinely used at the study ward and was the reference instrument for testing the responsiveness of the OMNI. As with all oral mucositis instruments currently used, a substantial overlap in OMNI and DMS items exists (table 1). The DMS involves scoring the presence of lesions, erythema, oral oedema, pain and dysphagia individually as 0 if absent, 1 if mild, 2 if moderate and 3 if severe.
Important differences between the two instruments are the use of a visual analogue scale for pain in the OMNI, and inclusion of an item on dryness of the mouth in the OMNI versus an item on dysphagia in the DMS. Also, the scale used for the erythema item differs for the two instruments.
Unlike the OMNI, the DMS allows for a transformation of the total score (range 0-15) into four oral mucositis grades to convey the severity of oral mucositis in a more accessible manner as has previously been reported by Donnelly et al.[2]. Hence the absence of oral mucositis was allocated an overall grade 0, while a score o 1-7, 8-14 and ≥15 was labeled respectively as grade 1 or mild mucositis, grade 2 or moderate mucositis and grade 3 or severe mucositis. These grades were used in our study and are referred to as the 'oral mucositis grades' in the analyses.

Table 1: *Oral Mucositis Nursing Instrument versus Daily Mucositis Score*

Item	OMNI	Levels	DMS	Levels
Lesions	Yes	0,1,2,3	Yes	0,1,2,3
Erythema	Yes	0,1,2	Yes	0,1,2,3
Oedema	Yes	0,1,2,3	Yes	0,1,2,3
Pain	Yes	VAS 1-10; 0,1,2,3	Yes	0,1,2,3
Dryness	Yes	0,1,2,3	No	-
Dysphagia	No		Yes	0,1,2,3
Score	-	Sum 0 - 14	-	Sum 0 - 15
Grades	No		Absence of oral mucositis is 0 1–7 is grade I or mild mucositis 8–14 for grade II or moderate mucositis ≥15 for grade III or severe mucositis	

Statistical analysis
Responsiveness was analysed using two strategies: Guyatt's Responsiveness Index and the Receiver Operating Characteristic (ROC) curves. Clinically important deterioration

or improvement in mucositis was assumed to have occurred if the oral mucositis grade increased or decreased respectively, by one grade, representing a shift from absent to mild, from mild to moderate, and from moderate to severe mucositis or the converse. Accordingly, a minimal clinically important change in the OMNI was defined as the mean change in the OMNI of patients who experienced a change in a single grade on the DMS. The Guyatt Responsiveness Index (GRI) i.e. the ratio of the minimally clinically important change in the OMNI and the standard error of this change was estimated[6]. We calculated three 'single step' GRI's for the transition between grade 0 and grade I, between grade I and grade II and between grade II and grade III. The standard errors with respect to the transition between grades I and I+1 are given by $\sqrt{MSE_i + MSE_{i+1}}$ in which MSE_i is the mean squared error of the OMNI obtained from one way analysis of variance (ANOVA) one repeated observations in patients with oral mucositis grade I. We defined the average of these three 'single step' GRI's as the final Gyuatt responsiveness index.

Values of <0.20, 0.50, and >0.80 representing respectively, slight, moderate, and large responsiveness,[8, 12] were used as references.

The second strategy to assess responsiveness of the OMNI instrument made use of the Receiver Operating Characteristic curves (ROC)[13, 8]. Briefly, responsiveness to improvement was described in terms of the sensitivity and specificity which were used to plot a ROC curve so as to assess the ability of the OMNI to reflect day-to-day improvement or deterioration. The area under the ROC curve represents the probability that the OMNI correctly classifies patients as improved or not when compared to the foregoing day. A second ROC analyses was performed to assess the responsiveness of the OMNI to deterioration.

The development of mean OMNI scores and mean grades between day 7 and 28 after conditioning were studied using linear mixed models with the aim of excluding possible delays in the OMNI response compared to the mucositis profile over time as expressed by the grade. The responsiveness per item was calculated and values of <0.20, 0.50, and >0.80 were again used to indicate slight, moderate, and large responsiveness.

Finally, Guyatt's index and AUC, and the ROC were calculated for all five resulting combinations of OMNI to explore the effect of simplifying the instrument by omitting a single item on the responsiveness.

Results

The onset and duration of oral mucositis of 32 patients is shown in Figure 1. The spread of the OMNI scores shows the variation in the severity of oral mucositis experienced by patients. Although most of the patients suffered from moderate mucositis between day 17 and 21 some had only mild mucositis whereas others suffered severe mucositis in the same period.

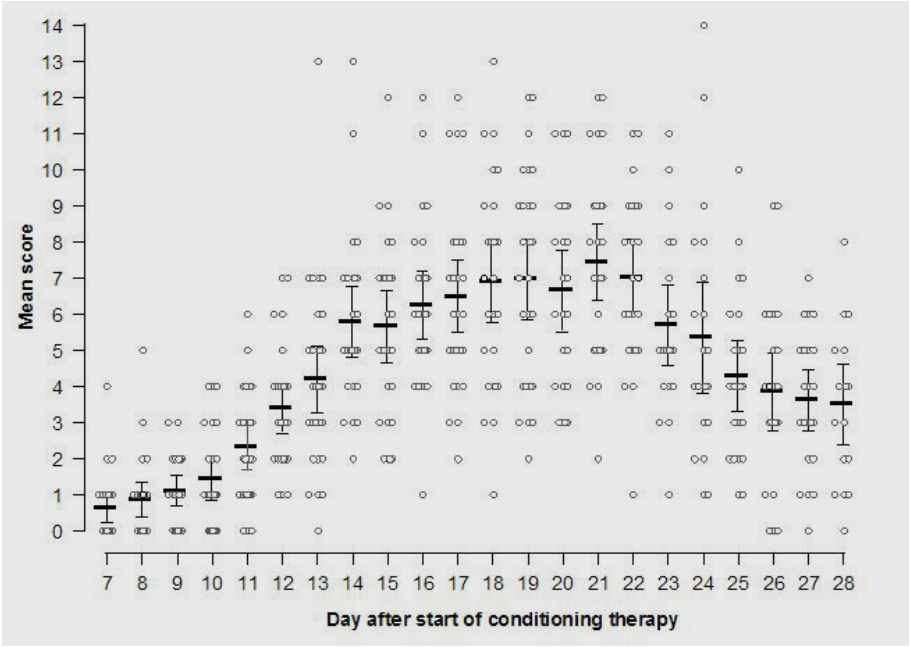
Guyatt's responsiveness index for the OMNI was 2.2 indicating a high sensitivity for detecting the change in oral mucositis over time. The ability of the OMNI to detect day-

to-day deterioration (or improvement) was also expressed by the areas under the two corresponding ROC curves which were 0.89 and 0.92 respectively. The development over time of the mean OMNI scores between the day of conditioning and the 14th day after HSCT was best described by a fourth-degree polynomial of the variable 'time from transplantation' (Figure 2). Mucositis began around day 7, becoming progressively more severe and reached a maximum on day 19. Thereafter the mucositis score decreased. The mean grade is conspicuously flatter than is the OMNI line showing the instrument to be highly sensitive to changes on a day to day basis.

Table 2 shows the responsiveness of Guyatt's index and the AUC ROC per item. Guyatt's index indicated large responsiveness per item whereas the AUC ROC values indicated a moderate responsiveness. The responsiveness of pain also contributed least to the OMNI compared to the other items.

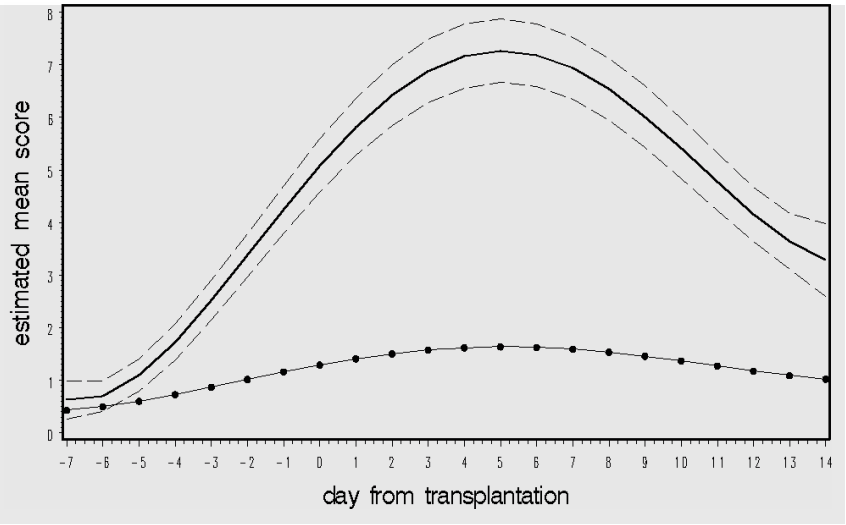
Reducing the instrument by one item had no marked influence on the responsiveness of the instrument as all values were ≥ 80 indicating greater responsiveness.

Figure 1: *Actual mean score*



The scatter plot shows the actual scores of the daily OMNI per day. The spreading of the OMNI score shows the variation of the severity of oral mucositis experience by patients. The box plots shows pattern of the daily OMNI scores

Figure 2: *The development of OMNI and the DMS over time*



Mean OMNI profile (—) with 95% confidence bands (---) and mean DMS grade (line with dots) as modeled with 4th degree polynomials using linear mixed models.
Day 0 is the day of hematopoietic stem cell transplantation.
Day –7 start of conditioning.

Table 2: *Effect of reducing the number of OMNI items on the responsiveness with five possible combinations.*

Instrument	Index of Responsiveness (Guyatt)	AUC ROC (Deterioration)	AUC ROC (Improvement)
P+D+E+L+O *	2.2	0.89	0.92
Four items			
P+D+E+L	2.0	0.86	0.87
P+D+E+O	2.2	0.88	0.90
P+D+L+O	2.1	0.87	0.90
P+E+L+O	1.8	0.85	0.90
D+E+L+O	2.2	0.87	0.90
mean	*2.1*	*0.87*	*0.89*
One item			
Pain	0.9	0.71	0.73
Dryness	1.0	0.68	0.70
Erythema	1.3	0.70	0.68
Lesions	1.0	0.66	0.71
Oedema	1.1	0.72	0.75
mean	*1.1*	*0.69*	*0.71*

P: pain; D: dryness; E: erythema; L: lesions; O: oedema
*: The original OMNI instrument.
Values of <0.20, 0.50, and >0.80 indicate small, moderate, and large responsiveness.

Discussion

In this study the responsiveness of the OMNI was shown to be good according to Guyatt's Responsiveness Index and the Receiver Operating Characteristic curves. These findings indicate that the OMNI is a good scale for measuring oral mucositis on a daily basis between day 7 and 28 after transplantation. Progression of mucositis is clear from figure 2, but this does not necessarily mean that the score for each individual patient can be predicted.

We explored the possibility of downsizing the instrument by a single item without loss of responsiveness and the results showed that four items are necessary to attain the most sensitive assessment of oral mucositis. Moreover, not one item could be omitted since each combination yielded a good responsiveness score.

However, there may be compelling arguments for simplifying the instrument. The usability of the OMNI was tested in a previous study and showed erythema and oedema to be the most difficult to assess among 63% and 72% of the nurses respectively. The weighted Cohen's Kappa coefficients were 0.60-0.26 underlining the nurses' expectations[11].

The validity of scoring pain is compromised when analgesia is used. None the less, pain is the most direct guide to the severity of oral mucositis and the consequent requirement for analgesia. In spite of the fact that erythema, oedema or pain could be deleted from the instrument without compromising responsiveness, there are no good arguments in terms of content validity to delete any one of these items. Each contributes to the total picture of oral mucositis and is consistent with the findings in a systematic review[11] which showed that experts generally include these items in instruments for monitoring oral mucositis. Therefore we propose not to change the instrument in our hospital, at least for the time being. However, those centres with nurses who are unfamiliar with assessing oral mucositis could choose to reduce the instrument by leaving out the more troublesome items erythema or oedema without seriously compromising the responsiveness of the instrument, as the quality of assessment depends on experience and nurses' training.

Our instrument was tested in a group of HSCT recipients admitted to a specialist ward. Therefore it should be tested in other settings before being generally adopted for patients who receive other cancer therapies.

Ideally, responsiveness is assessed by comparing the results of the test under consideration to the results of an instrument that is known to be responsive[6]. In the present study, such an approach was not feasible simply because there is no gold standard for measuring oral mucositis.

Until now, most attention concerning responsiveness has been devoted to following changes indicating improvement. The OMNI is able to monitor the course of oral mucositis which gets worse before it gets better as the score gradually increased reaching a maximum in the 2nd week after stem cell infusion declining thereafter as oral mucositis improved.

Investigators using instruments that are not responsive could falsely draw negative conclusions from the results of their clinical research. Therefore it is important to have

an instrument that is capable of detecting small but relevant and important changes especially when the outcome of interest is also the primary outcome measure for a trial [14, 15]. Furthermore, in the design of a clinical trial on oral mucositis, researchers must be confident that the score used is responsive enough to detect the minimal important difference that is hypothesized[16]. In the literature only two studies have reported the responsiveness of their instrument. Sonis et al.[17] concluded that his instrument was responsive over time, but a definition of responsiveness and how it was quantified was not reported whilst Stiff et al.[18] calculated responsiveness extensively and found the daily questionnaire administered by the patients themselves was responsive.

In conclusion, we have shown that the OMNI is responsive to alterations in oral mucositis and encourage other researchers to evaluate their instruments in the same manner.

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Chapter 5

Providing oral care in haematological oncology patients: Nurses' knowledge and skills

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Abstract

In the international literature, the most commonly recommended intervention for managing oral mucositis is good oral care, assuming that nurses have sufficient knowledge and skills to perform oral care correctly.
The aim of the present study was to investigate if knowledge and skills about oral care improve when education in oral care is provided to nurses in charge of patients who are at risk of oral mucositis.
This intervention study consists of a baseline test on the knowledge and skills of nurses of the haematology wards of two different hospitals. Oral care education sessions were given in one hospital and follow-up tests were performed in both hospitals. Nursing records were examined and observations of nurses performing oral care were made at baseline as well as at follow-up.
The results show significant differences in the scores for knowledge and skills before and after the education, whereas there was no difference in scores at the two points in time for the comparison hospital, where no education had taken place. The records test showed no differences at baseline or follow-up for the two groups. Observations showed that nurses who followed the education session implemented the oral care protocol considerably better than those who did not attended.
Education in oral care has a positive influence on the knowledge and skills of nurses who care for patient at risk of oral mucositis, but not on the quality of oral care documentation.

Introduction

Patients who receive chemotherapy to treat malignant disease, often experience oral mucositis as the most debilitating side effect [1, 2]. As a result of oral mucositis, patients' quality of life can be affected by pain, infection, altered nutrition and impaired oral function [3, 4]. Oral mucositis is one of the most common causes of treatment delay and dosage reductions in cancer therapy [5].

Prevention and treatment are as important to oral mucositis as they are to fatigue, nausea and vomiting and many other side effects affecting patients with cancer.

Nurses play a central role in preventing and managing oral mucositis and reducing its debilitating effects on patients. In fact they have 3 main tasks in managing oral mucositis: (1) assessing and monitoring changes in the oral cavity; (2) providing appropriate oral care; and (3) offering patient education [6].

Nurses give oral care of patients with cancer a high priority [7], but very little is known on day -to -day practice [8].

In the international literature, regular oral care is most commonly mentioned for managing oral mucositis [9-11] though the standards for oral care are not consistently implemented and advice on the frequency of oral care frequency varies from 'once every shift' to 'only if patient requests it'.

Furthermore, obstacles to providing oral care have been little investigated. McGuire [12] outlined barriers to implementing oral care standards and proposed strategies to overcome them. In a study by Wallace et al. attitudes and subjective norms predicted 39% of the behaviour of nurses in providing oral care [13].

Simple lack of knowledge about oral care is a major barrier to providing optimal oral care [12]. A first and necessary step in the process of change is to identify the educational needs that exist in order to be able to offer adequate education and support, both theoretically and practically. However, knowledge deficits are not the only barriers. To manage oral care effectively, nurses require more and continuing education [7, 8].

An important part of daily oral care is to assess the oral cavity of each patient at risk for oral mucositis. To this end, nurses should be trained in the use of standardised tools for screening and assessment [14] in order to be proficient in using such instruments [15]. Besides this, training increases the inter-observer reliability of the oral assessment and improves the evaluation of mucositis [16].

The aim of the present study was to investigate whether knowledge and skills regarding oral care improve when education is provided to nurses caring for patients who are at risk for oral mucositis.

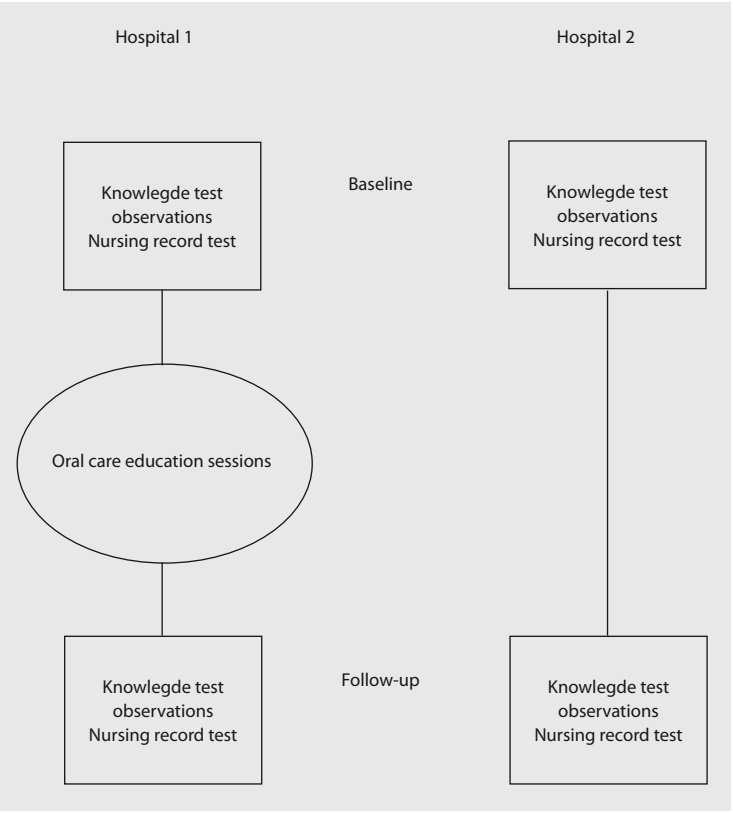
Methods

Study design

Baseline tests on the knowledge and skills of nurses in haematology wards of two different hospitals were conducted. Oral care education sessions were given in one hospital

and follow-up tests were performed in each hospital (Figure 1).
The baseline and follow-up consisted of performance observations as well as the nursing record tests. A knowledge test was also employed to investigate nurses' familiarity with the key principles of oral care. Oral care education sessions were tailored to the baseline scores. The follow-up tests were performed one month after the last education session in the intervention hospital.

Figure 1: *study plan*



Setting and sample
The study population consisted of nursing staff of the haematology wards of two university hospitals in the Netherlands. The intervention group was made up of qualified nurses experienced in nursing on the haematology ward of the Radboud University Nijmegen Medical Centre (RUNMC). The ward has 28 patient beds and admits 100 patients a year for autologous and allogeneic HSCT. The Daily Mucositis Score (DMS) [17] was used to assess oral mucositis on a daily basis. Briefly, this requires the nurse to score erythema, oedema, dysphagia, lesions and pain assigning a score of 0 to 3 on a specially designed chart containing each day of the week.

Nursing staff developed an oral mucositis care plan when the first signs of oral mucositis appeared which consisted of brushing the teeth four times daily using a soft toothbrush and using oral rinses with normal saline (0.9% NaCl) or water.
The control group consisted of experienced nurses from the haematology/oncology ward of the Academic Medical Centre of Amsterdam (AMC). The ward has 18 haematological beds and admits 60 patients a year for autologous and allogeneic HSCT. Patients admitted to this ward received an oral care regime similar to that included in the RUNMC care plan. Oral inspection was done every day for patients at risk for oral mucositis without employing a specific assessment instrument. Signs of oral mucositis were recorded, though not in a standardised manner and a checklist was used to monitor daily oral care.
The protocols of both wards were based on published guidelines including those of the MASCC [11, 18].
The intention was to examine 60% of the nurses per ward at both baseline and follow-up. All nurses were informed that participation was voluntary, and their anonymity was guaranteed.

Instruments and procedures
Demographic data were collected on gender, age, years of nursing experience and basic nursing degree.

Knowledge test
The knowledge test was a 32-item questionnaire including open-ended and multiple-choice questions and 8 photographs of the mouth illustrating different stages of oral mucositis. A team of experts including a haematologist (NB), nurse specialist (CP), dental hygienists (AO, MO) and an oncology nurse (AM) developed the test from existing protocols, the international literature and their own specialized knowledge.
Topics included:
- Anatomy and pathology of the oral cavity (10 open questions, max. score 123 points).
- Oral hygiene (10 open questions, 3 multiple-choice questions, max. score 166 points).
- Oral mucositis (4 questions, max. score 45 points).
- Patient education (5 open questions, max. score 76 points).
- Assessment of oral mucositis in 8 photographs, (max. score 40 points).

The overall maximum score was 450 points. On average, 30-45 minutes were needed to complete the test. In the intervention hospital, only the nurses who had received these sessions were asked to participate in the follow-up test.

Observation of skills
The observations were designed to evaluate nurses' oral care skills. A list consisting of 44 observations points (OP) was developed to audit these activities and each was answered with 'yes' (done) or 'no' (not done). The OP were grouped into 5 subsections;
- Checking patient's oral status of the previous days (3 OP)
- Assessment of the patient's oral cavity according to the protocol (12 OP)

- Assisting with or performing oral hygiene for the patient (23 OP)
- Patient directed advice for oral care (3 OP)
- Documentation of findings in the nursing record (3 OP)

The maximum score was 44 points. The list was a mix of the standardised protocols of both hospitals, though some questions were not relevant for both settings (e.g. locally standardised preventive or treatment prescriptions).
The observations at both baseline and follow-up were done during the day by examining the mouths of patients known to have oral complaints. Two dental hygienists observed the nurses while they assessed the oral cavity and delivered oral care.

Nursing record test
Correct and adequate reporting of findings and interventions is essential to nursing care. The nursing record test consisted of six questions derived from the hospital protocols:

- The status of the oral cavity is recorded daily;
- Results of oral assessment are reported;
- The patient's oral pain is recorded;
- In case of signs of oral mucositis, the oral care protocol is started;
- Advice concerning oral care is provided to the patient and documented;
- Interventions are started and documented.

Ten nursing records from each ward were reviewed in retrospect, both at baseline and follow-up. Each question was assigned a maximum of 4 points and the completeness of the records was given up to 24 points.

Oral care education sessions
The oral care education sessions were offered to the nursing staff of the RUNMC only. The results of the baseline knowledge tests directed the content of these sessions.
The training was given by two dental hygienists who provided theoretical education on the anatomy of the oral cavity, relevant pathology, oral hygiene, oral mucositis and options for prevention and treatment. Oral assessment training was achieved with the help of slides. A second component of the training consisted of nurses cleaning each other's teeth, which helped them rehearse their skills and experience the process from the patient's perspective. The education session took 1½ hours. Four identical sessions were offered to enable as many nurses as possible to attend.

Statistical analyses
The tests on the nursing record, nurses' knowledge and the skills performance observations resulted in summary scores and were analysed using the Statistical Package for the Social Science (SPSS version 14.0) using simple descriptive statistics. A total score for both tests was used to give a final analysis of nurses' knowledge, skills and performance in documentation.
The effect of the intervention (education sessions), compared to no intervention was analyzed using two-way independent 2^2 ANOVA. A significant (alpha=0.05) interaction

of the main effects for time point (baseline versus follow-up) and group (intervention versus control) was to indicate a positive effect of the education sessions.

Results

Knowledge test

Thirty-one and 29 nurses participated in the knowledge test at base line and at follow-up respectively. Two nurses of the control group started the knowledge test but did not finish it. Their tests results were not analysed. Nurses were predominantly females, with a mean age of 34.9 years (range 24-54) and a mean number of 6.2 years (range 1-15) of experience in care of oncology patients (Table 1).

Table 1: *Nurses' age and experience for both nursing teams at both time points*

	Intervention group baseline	Intervention follow-up	Control group baseline	Control group follow-up	Total
N	20	20	11	9	60
Mean age (years)	36.4	34.9	36.6	31.9	34.9
Mean experience (years)	7.6	5.9	5.7	5.6	6.2

At baseline, only 30% of the nurses knew all the characteristics of mild mucositis, whereas 60% of the nurses were able to describe severe mucositis. Most of the nurses knew the most important risk factors for development of oral mucositis. On the other hand, only half of the nurses gave correct answers to the questions on anatomy and pathology. Knowledge about oral hygiene varied, with more than 50% of the nurses being unable to offer advice to a patient with dental prostheses and oral mucositis. Three out of eight photographs showing various stages of oral mucositis were assessed correctly by 75% of the nurses. The test was a revelation to some nurses as it showed how little they knew about aspects of oral mucositis.

Table 2: *Knowledge test mean score and standard deviation per group and time point*

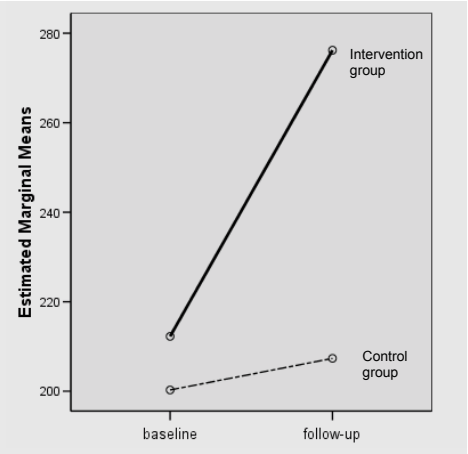
	Intervention group baseline	Intervention group follow-up	Control group baseline	Control group follow-up
N	20	20	11	9
Mean	212.3	276.2	200.3	207.3
Std. deviation	36.9	35.5	43.2	34.9

The difference in mean increase is 56.9, 95%CI: [15.7; 98.0], $p = 0.008$

Table 2 shows the means and standard deviations on the knowledge test for the two groups and both points in time. There was a significant interaction effect (illustrated in figure 2) between time (baseline versus follow-up) and group (control versus inter-

vention): $p = 0.008$. The difference in the increase in mean knowledge was 56.9, 95%CI: [15.7; 98.0], indicating a relevant positive effect of education on knowledge (Figure 2).

Figure 2: *Esimated marginal means of total score knowlegde test.*



Observation of skills performance

The results of the observation test are shown in Table 3 (to facilitate the interpretation of the results, the maximal score per section is presented next to the actual scores).
At baseline, almost half of the nurses assessed the patient's oral cavity without knowing the previous oral status. Many mistakes (50%) were made with oral inspection The equipment required was not always used, and the floor of the mouth was overlooked in two-thirds of cases. However, 65% of the nurses gave at least some advice about oral care to the patients.

Table 3: *Observations mean scores per item and overall mean score and standard deviation per group*

	Intervention baseline N=10 Mean	Intervention follow-up N=10 Mean	Control baseline N=10 Mean	Control follow-up N=10 Mean
Checking patient's oral status of previous days before oral assessment.	4.5	5.6	5.0	2.7
Assessment of patient's oral cavity according to the protocol.	15.8	21.9	15.2	15.3
Assisting with- or performing oral hygiene for the patient.	32.4	39.5	29.8	34.2
Patient directed advice for oral care	5.2	5.8	4.4	5.1
Documentation of findings in the nursing record.	2.7	2.7	2.6	2.3
Overall Mean	60.6	75.5	57.0	59.6
St. deviation	9.0	5.6	7.9	8.8

The difference in mean increase is 12.3, 95%CI: [2.1; 22.5], $p = 0.019$

Nurses who attended the oral care sessions implemented the oral care protocol significantly better than those who did not attend ($p = 0.019$). The difference in mean increase in total score was estimated at 12.3, 95%CI: [2.1; 22.5].

Nursing record test

Only records of patients at risk for oral mucositis were included in the nursing record test. Each record was carefully studied by two dental hygienists with the help of the checklist (Table 4). There were no significant overall differences between the groups $p = 0.367$. The difference in mean increase in total score was estimated at 2.3, 95%CI: [- 2.9; 7.5].

Table 4: *Record tests mean scores per item*

	Intervention group baseline N= 10	Intervention group follow-up N=10	Control group baseline N=10	Control group follow-up N=10
A daily notation concerning the status of the oral cavity is written	1.2	0.9	1.3	1.9
Results oral assessments are reported.	1.2	2.7	2.4	1.9
Patient's oral pain is recorded.	0.8	0.8	1.0	0.8
If there are signs of oral mucositis, the oral mucositis protocol is started.	2.6	2.3	1.7	1.3
Advice concerning oral care is given to the patient and is recorded.	1.1	2.4	1.7	1.6
Interventions are started and recorded.	1.4	1.1	1.0	1.2
Overall Mean	8.3	10.2	9.1	8.7
St. Deviation	4.3	4.0	4.5	3.3

The difference in mean increase is 2.3, 95%CI: [- 2.9; 7.5], $p = 0.376$.

Discussion

The aim of this study was to investigate whether knowledge and skills in oral care improve when education is offered to the nurses who care for patients at risk for oral mucositis. Nursing skills were assessed by reviewing nursing records and observing nurses while they were providing oral care. Furthermore, knowledge tests at baseline and at follow-up provided a clear impression of the effect of oral education sessions.

To our knowledge, this particular study design has not been used previously, though there are a number of studies in other areas that used educational interventions to

change knowledge and skills. For example, Dalton et al. [19] designed an educational program to improve knowledge in order to change pain management practices and patient outcomes. This program was offered to nurses who provided day-to-day care for patients with cancer. A quasi-experimental design was used to measure the effectiveness of the program in changing nurses' knowledge, attitude and behaviour. Data were collected from nurses and patient charts before and after the program. Nurses' knowledge improved, but the change was not statistically significant.
In contrast with the study by Dalton and similar studies on the effects of education in nurses, our study added observations on performance, a less common element in this type of study.

Knowledge tests
In our study, we tested the actual knowledge of nurses in the area of oral care. This is in contrast to other studies that investigated nurses' self-reported knowledge or personal views on oral care by means of questionnaires or interviews [7, 8, 20, 21]. Nevertheless, the results are similar; baseline data revealed that nurses have gaps in their knowledge of oral care, particularly in their knowledge and assessment of the different stages of oral mucositis.

Observation of performance
At baseline, observations of nurses carrying out oral care revealed mistakes in assessing the oral cavity as well as in assisting with- or providing oral hygiene. Moreover, even though oral assessment had become a daily routine, procedures that were wrongly learned, persisted.
Observations by dental hygienists during the daily nursing routine are not common for nurses or their patients, which will alter their behaviour as they know that they are being watched. This could have resulted in more favourable scores for nurses. However, as observations were used at both points in time, the changes from baseline identified in our study are likely to be genuine. Follow-up data showed significant improvement of oral care given by nurses who attended the oral care sessions indicating that quality of oral care will likely be improved by refreshing existing knowledge and providing new knowledge.

Nursing records
The purpose of the nursing record is to have an easily accessible reference that describes the patient's needs and wishes. Also, nursing interventions can be documented and evaluated in the record[22]. The records are the main source of information on each patient's oral care.
At baseline, the results for the record test showed inadequacies in the documentation of oral care. Most of the records were incomplete and sometimes oral assessment was documented but the accompanying intervention was not described. Although special attention was given to this during the education sessions, the follow-up test showed no improvement in the quality of the records. This likely reflects a more general attitude of nurses towards reporting. To improve the quality of nursing records, a more

comprehensive training should be provided, together with continuous feedback based on regular evaluations [23]. The development of electronic nursing records might possibly improve accuracy and make them a more useful source for information on patient outcomes [24].

Oral care education session

The effects of educational sessions showed the impact of education and training. Training in oral assessment is necessary, even for experienced nurses, to prevent mistakes when inspecting the oral cavity and to ensure the results are judged correctly [15, 16]. During the education sessions, slides of photographs of the mouth showing different stages of oral mucositis were used. In future studies, videotaped demonstrations [25] and guided practice in assessing patients' mouth under supervision of an experienced nurse or a dental hygienist could optimise the trainings. The practical part of the education sessions consisted of nurses brushing each other's teeth. This 'simple' task was regarded as unpleasant but after the session many nurses changed their attitude towards the cleaning of teeth.

Limitations

The tools used in this study were specifically designed for this study and were not extensively tested for their validity and reliability beforehand. However, the record test was based on expert validity and only two observers used the observation and the nursing record tool and they fine-tuned their interpretation to provide greater consistency.

The follow-up data were collected one month after the education sessions so we do not know whether the same results would be obtained after 6 months or later.

Our study included two wards of two different hospitals which, though similar in admission policy and patient demographics, will likely differ in other aspects. In addition, paired analysis was not possible because of the anonymity of the participants. The sample of nurses was different pre- and post-test which could have introduced bias into our study.

Generalizability is also limited as our study was conducted in only two haematology wards in the Netherlands. It is therefore not certain whether the results can be generalized to haematology wards in other centres or general oncology wards and outpatient clinics here in the Netherlands or indeed elsewhere. None the less, the literature does suggest that similar problems and challenges exist elsewhere [7, 8, 20, 21, 26, 27].

Conclusion

Knowledge and skills improve when education in oral care is given to nurses. Baseline data showed a lack of knowledge and skills concerning oral care. These data gave direction to the need for and desired content of education sessions. Our education sessions met the need for oral care knowledge among nurses.

Recommendations

Regular oral care education sessions to improve or refresh oral care knowledge, are

the most important recommendation from this study. Audits and feedback are likely to improve oral care skills in practice. Senior nursing staff should consider selecting interested and experienced nurses to become 'resource nurses in oral care'. They can act as advisors, an information source and counsellor on oral care at the ward. These nurses should be responsible for oral care education sessions and they can also supervise and teach oral assessment and care in clinical practice.

Follow-up studies are necessary to validate our findings, and to determine the most effective training interval and type of instruction and research is needed to determine the impact of knowledge on patient outcomes.

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Chapter 6

Guidelines for the assessment of oral mucositis in adult chemotherapy, radiotherapy and haematopoietic stem cell transplant patients

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Abstract

Oral mucositis (OM) is a serious consequence of some chemotherapy and radiotherapy regimens. A number of reliable instruments are available to assess OM, but none are universally accepted. A unique collaboration of multi-disciplinary experts from Europe was formed to make recommendations on OM assessment, based on a systematic literature review and the experts' experience. The main recommendations are listed. There should be a comprehensive baseline assessment. OM should be frequently assessed using a standardised instrument, or a combination of instruments. Physical, functional and subjective changes should be measured. Subjective measures should be assessed prior to any physical examination. The use of pain scoring, in particular patient self-reporting, should form part of any OM assessment. Any assessment instrument should be validated, easy to use and comfortable for the patient. Training of, and monitoring in, the use of the instrument is vital to successful monitoring of OM.

Introduction

Oral mucositis (OM) is a frequently distressing, and sometimes serious, consequence of treatment with certain types of cancer therapies, with an incidence ranging from 15% to 90%.[1-3] OM is a multistage biological process that can cause erythema, swelling, bleeding and painful ulceration of the mucosal tissue.[4]

The impact of OM is generally under-rated, although patients often cite OM as one of the worst side effects of their treatment[6,7]. Recent studies also show that severe OM is associated with inferior overall survival following haematopoietic stem cell transplantation (HSCT)[7]. OM impacts on healthcare costs, due to increased length of in-patient stays and demands on resources[8,9]. The prevention and palliation of OM is a priority for those involved in the management of these patients. The Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) guidelines provide clinicians with a comprehensive assessment of OM prevention and treatment protocols and make recommendations for best clinical practice[10,11]. Diagnosing and grading the severity of OM forms the basis of management and, accordingly, a number of validated and reliable instruments are available for this purpose[12].

Their individual limitations, however, often lead investigators and clinicians to adapt existing scales or develop new ones. Unfortunately, there is a lack of consistency amongst these scales, and consequently, none are universally accepted[1]. It is the absence of a universally accepted assessment scale, the lack of guidelines on best practice in OM assessment and the use of inconsistent and incompatible OM assessment instruments that continues to hinder progress in the measurement and management of this condition.

Nursing, medical and dental experts from the European Group for Blood and Marrow Transplantation (EBMT) and the European Oncology Nursing Society (EONS) convened to form the Oral Mucositis Assessment Guidelines (OMAG) taskforce to generate guidelines for the use of tools in assessing OM in the adult patient with a malignancy. The aim of the taskforce was not to develop another tool, but to thoroughly analyse the assessment instruments currently available, their implementation and to formulate recommendations with which to address inconsistencies in the assessment of OM.

Methodology

Literature search

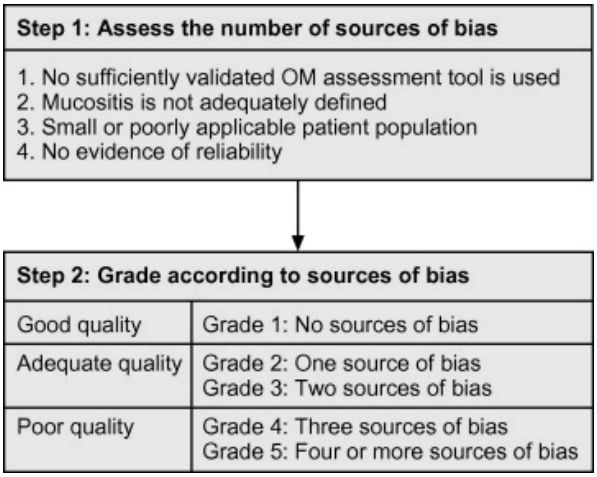
The methodology is similar to the one used in the recent guidelines from the United Kingdom Children's Cancer Study Group (UKCCS) and the Paediatric Oncology Nurses Forum (PONF) Mouth Care Group (UKCCS-PONF guidelines)[13] .

Questions considered pertinent to OM assessment were defined by the EMBT/EONS OMAG taskforce (Appendix 1). Search terms were defined and MEDLINE, EMBASE and the Cochrane Library were searched electronically (Appendix 2). To be considered relevant, the studies had to be phase II or III original clinical studies published in English

between 1st January 1990 and 31st January 2006, and involve patients ≥ 18 years of age. Studies were included if OM was a primary endpoint or if they compared OM assessment tools. Additional papers not identified in these electronic searches were suggested by members of the taskforce.
Relevant articles in press were identified by searching for abstracts on conference websites (Appendix 2). Abstracts that met the inclusion criteria were compared against papers already identified in the electronic literature search and papers recently published through PUBMED. If data from the abstracts had not been published, the first author was contacted to see if the paper was in press and could be included in this analysis.

Evidence assessment
A system for grading the quality of individual studies was adapted from frameworks of diagnostic test accuracy tools[14-19]. Each study was graded according to the number of predefined sources of bias in the study design (Fig. 1). The quality of each study was then rated as good (Grade 1), adequate (Grades 2 and 3) or poor (Grades 4 and 5).

Figure 1: *Studies were assessed for bias and graded accordingly*



The papers were then reviewed for evidence to support or counter each of the taskforce's questions and the overall evidence that answered each question was then rated, according to the following criteria:[15-20] quantity – rated as a high (>10), moderate (3–10) or low (≤ 2) number of studies; consistency – the extent to which similar findings were reported, rated as good or poor; generalisability – how reasonable it is to apply the results of these studies to the target population, rated as good or poor; and clinical applicability – the potential clinical impact of the findings, rated as good or poor. Finally, the strength of the body of evidence behind each recommendation was deduced as shown in Table 1, and the recommendation was graded.

Table 1: *Grading of evidence for recommendations*

Quality and quantity of studies in body of evidence	Consistency, generalisability and clinical applicability of evidence	Strength of evidence	Strength of recommendation
High/moderate number of good-quality studies *or* High number of adequate-quality studies	→ All good	→ Strong	→ Strongly recommended
High/moderate number of good-quality studies *or* High number of adequate-quality studies	→ One or more are poor	→ Sufficient	→ Recommended
Moderate number of adequate-quality studies *or* Low number of good-quality studies	→ All good	→ Sufficient	→ Recommended based on expert opinion
None of the above criteria met	→	Insufficient	→ Available studies do not provide sufficient evidence to formulate a guideline

The evidence for each recommendation is grouped, and the overall strength of the recommendation is graded according to the quality and quantity of studies providing evidence and the consistency, generalisability and clinical applicability of the body of evidence.

The evidence for each recommendation is grouped, and the overall strength of the recommendation is graded according to the quality and quantity of studies providing evidence and the consistency, generalisability and clinical applicability of the body of evidence.

Definition of therapy

For the purposes of these guidelines, the term 'therapy' meant the administration of a cycle of radiotherapy (RT), chemotherapy (CT) or the period of conditioning treatment prior to stem cell transplantation.

Results and discussion

Literature search

A total of 57 papers, most of which were research studies, met the inclusion criteria and addressed at least one of the questions (Appendix 1)[7-12, 21-75]. The findings from the collation of evidence and the corresponding strength of evidence are covered for each recommendation below.

Recommendation 1: *use of a standardised procedure for assessment*

OM should be assessed using a standardised protocol.
Evidence: strong/sufficient, therefore (strongly) recommended.

Commentary on recommendation 1: use of a standardised procedure
Standardised procedures are defined here as OM assessment protocols that followed validated assessment tools (i.e. the tools and their validation studies were referenced in the paper), explicitly described the assessment procedure, or at the very least, outlined the frequency of assessment and defined the healthcare professionals involved.
A total of 22 different assessment tools were used in the papers that provided evidence for this recommendation. Only two[47,74] out of 57 eligible studies did not describe the OM assessment protocol in sufficient detail. Eleven studies[12,23-29,40,43,55,64,73] used well-described self-developed or modified instruments. Table 2 lists all the tools (excluding self-developed scales except where the studies were for the express purpose of developing a scale), and the elements used in assessing OM. Pain, erythema and ulceration are the most commonly used measures across the tools.
The World Health Organisation (WHO) scale was the most frequently used in the included studies (12 studies) [21,24,29,39,48,49,52,56,60,65,69,72]. Of these studies, 10 were graded Grade 1 or 2,[21,24,29,39,48,49,52,60,65,69] showing that despite its simplicity, this scale does not limit study quality.
The Oral Assessment Guide (OAG) scale was the second most frequently used. Although the Oral Mucositis Assessment Scale (OMAS) or Oral Mucositis Index (OMI)-based scales were specifically developed for OM staging, few studies in this analysis employed these tools, probably due to their complexity in clinical practice.
Four studies compared two scales in parallel, particularly for validation purposes. Good correlations were found between OMAS and National Cancer Institute Common Toxicity Criteria (NCI-CTC) scores[41], and the Western Consortium for Cancer Nursing Research (WCCNR) and MacDibbs Mouth Assessment scales[54]. Donnelly and colleagues[39] showed that a Daily Mucositis Score (DMS) achieved by adding scores for various elements of OM, was more successful than the WHO tool in monitoring OM through all its stages of development. Dodd and colleagues used several scales, and concluded that the tool must be chosen with the purpose of assessment in mind[35]. The taskforce recommends that this principle should be used when choosing the OM assessment tool.

Table 2: *Assessment tools and elements used*

Instrument - original or modified (number of studies)		WHO (12)	OAG (8)	NCI-CTC (7)	OMI (4)	MacDibbs (3)	OMAS (3)	Nebraska (3)	RTOG (2)	WCCNR (2)	CALGB (1)	DMS (1)	Kolbinson (1)	NCCTG (1)	Seto[64] (1)	Walsh[45] (1)	OMNI (1)
Physical changes	Erythema	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
	Ulceration	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
	Oedema		✓	✓	✓	✓		✓		✓	✓	✓				✓	✓
	Salivary changes		✓	✓		✓		✓		✓	✓					✓	
	Swallowing	✓	✓			✓		✓		✓		✓				✓	
Functional changes	Voice		✓			✓		✓								✓	
	Eating solid food	✓		✓		✓					✓			✓			
	Pain	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Lips		✓					✓								✓	
	Tongue		✓					✓								✓	
Sites	Mucous membranes		✓					✓		✓			✓			✓	
	Gingiva		✓					✓								✓	
	Teeth		✓					✓									
	Atrophy				✓												
	Pseudomembranes				✓												
	Lichenoid				✓												
	Hyperkeratosis				✓	✓											
	VAS				✓												
	Dryness					✓											
Other elements	Taste					✓											
	Hyperkeratosis																
	Sputum smear for fungus					✓											
	Herpes simplex culture					✓											
	Bleeding								✓	✓						✓	
	Soreness										✓						

Some scales, such as those that quantify oral changes, e.g. OMI and OMAS, are developed for research purposes rather than for patient care; the total number of studies is greater than 57 as some studies used more than one instrument. *Abbreviations:* WHO, World Health Organisation; OAG, Oral Assessment Guide; NCI-CTC, National Cancer Institute Common Toxicity Criteria; OMI, Oral Mucositis Index; VAS, Visual Analogue Scale; OMAS, Oral Mucositis Assessment Scale; Nebraska, Nebraska Oral Assessment Score; RTOG, Radiation Therapy Oncology Group Acute Toxicity Scoring; WCCNR, Western Consortium for Cancer Nursing Research; CALGB, Cancer and Leukaemia Group B; DMS, Daily Mucositis Score; NCCTG, North Central Cancer Treatment Group, NNMSS, Nijmegen Nursing Mucositis Scoring System.
[a] Nine oral sites in total.

Recommendation 2: *routine assessment of OM*

For a patient's OM to be managed, routine assessments should take place. Patient self-reporting should form an integrated part of the assessment.
Evidence: sufficient strength, therefore recommended.

Commentary on recommendation 2: routine assessment of OM
A total of 13 studies (two high-quality[52,64] and nine adequate-quality[32,34,37,39,48,50,51,71,75] provided evidence that frequent OM grading directed the active management of OM. In general, once OM scores passed certain thresholds, new, predetermined management strategies were implemented[9,37,60,71]. Interventions were usually initiated when OM was scored as moderate to severe. These studies used a total of nine assessment instruments, indicating that no single scale is particularly geared towards enabling clinical interventions.
Eiler's OAG was used in five of the 13 studies (Grades 2–4)[34,36,51,70,75]. This instrument scores OM when changes to the mucosa are first observed, thus allowing early preventative or analgesic interventions. It is essential that risk factors of OM, or OM itself, are recognised at an early stage so that adequate measures can be implemented[12]. Authors using OAG note that the tool enables clinicians to document daily changes in oral status, plan appropriate interventions and follow trends[75]. The tool was found to be understandable, required only 3–4 min to complete and was clinically applicable for oncology nurses[44].
Several studies by Dodd and colleagues[34,36,37] used an extension of the OAG, a thorough patient self-assessment programme (PRO-SELF Mouth Aware [PSMA] programme). The PSMA programme aims to support cancer patients with information on oral complications, self-care techniques and contact with nurses experienced in OM. Through this programme, patients learn the principles of good oral hygiene and how to thoroughly examine their mouth using assessment criteria based on the OAG[77].
It is the opinion of the taskforce that routine assessment of the oral cavity (both by patient and clinician) and information or educational programmes should ensure that the patient and healthcare professional are more aware of changes to the oral mucosa, the risks of OM and that patients are supported in improving their oral care practices[34,36,37,77].

Recommendation 3: *baseline oral assessments*

A comprehensive baseline oral assessment should be made prior to treatment, where OM is expected.
A further baseline assessment of OM should be taken as close to the administration of the first treatment dose as possible.

Evidence: sufficient/insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 3: baseline oral assessments

There is sufficient evidence that baseline assessments of the oral cavity should be made prior to any potentially damaging therapy. Only 17 papers[7,12,22,25,30-32,46,53,56,62,68,70-73,75] did not specify baseline readings, in some cases because patients had already received CT or RT prior to study entry.

The taskforce suggests two types of baseline assessment: one in preparation for the proposed treatment and the second immediately before treatment administration. The first should be a comprehensive examination by dentists to identify, and if possible address, pre-existing conditions and OM risk factors (e.g. dental or oral infection, broken teeth, periodontal disease or poor oral hygiene). The examination and treatment of pre-existing problems should take place as early as possible prior to initiation of therapy[78].

The second baseline assessment, conducted immediately prior to treatment, establishes a basis from which changes in the oral mucosa can be determined. In nine studies[22,23,31,32,39,58,59,69,74]. oral assessments only began on the day of stem cell administration, despite conclusive evidence that the onset of OM can occur during the conditioning phase of treatment[1,7,39,72,79]. Similarly, the onset of OM following RT can be rapid: for some head and neck patients, symptoms can be observed as early as the first day of RT[80-82]. It is therefore essential that baseline assessments are made before the onset of treatment.

Recommendation 4: *frequency of assessment*

4A – Frequent assessment of OM is recommended throughout the course of therapy, and especially for patients most at risk of developing OM. For outpatients, this will require some degree of self-assessment, although self-assessment for in-patients may also be beneficial.

Evidence: sufficient, therefore recommended.

4B – Assessment, whether by clinicians or patients, should take place on a daily basis during the period when OM is likely to first occur or be at its peak. Depending on the severity of baseline OM assessments and risk factors, assessments will need to continue at regular intervals (daily, every 2–3 days, weekly) as OM resolves.

Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 4: frequency of assessment

One of the unresolved issues of OM is the frequency of its assessment. In this analysis, the frequency of examinations during treatment varied from a four-times-

daily patient self-assessment[34] to weekly, but none of the studies looked specifically at the timing of assessments. Five good-quality studies[35,52,59,61,64] and 21 adequate-quality studies[7,21,23-25,28-30,33,37,41-44,49,55,56,58,60,68,73] support a frequency of a less than once-daily assessment compared with two good-quality[65, 66] and 17 adequate-quality studies[7,12,22,31,32,39,42,46,50,51,57,62,68,69,72,74] favouring a daily assessment.

The severity of OM can alter dramatically in 24–48 hours and symptoms can change depending on pain relief and other treatments; it seems prudent to conduct examinations every one or two days, particularly at times when it is likely to arise or when it is particularly severe or painful. The taskforce believes that, where patients are unable to maintain their oral health or require pain relief, daily assessment, including pain assessment, is essential.

In practice, it may be difficult to have such frequent assessments, especially in the outpatient setting where patients between treatment cycles may not be seen for several weeks. It is the opinion of the taskforce that all patients should be trained in self-assessment and report typical signs/symptoms to the healthcare team. The PSMA programme[34] is a good example of a self-assessment scheme that can be adapted for in- and outpatient use.

Recommendation 5: *post-treatment assessment*

OM assessments should continue until OM is fully resolved or the trend to resolution is established. If OM has not resolved on discharge, follow-up of the patient is recommended. In the in-patient setting, assessment should continue until OM is resolved, which in most cases is approximately 2–4 weeks after treatment.

Evidence: sufficient to strong, therefore strongly recommended.

Commentary on recommendation 5: post-treatment assessment

Once treatment is stopped, OM may continue to increase in severity before resolving[1,3,72,76]. Only 13 studies (one good-quality study,[35] nine adequate-quality[29,33,34,46,48,53,62,68,73] and three poor-quality[36,38,70]) covered post-treatment assessment in outpatients. Overall, the evidence favoured follow-up in outpatients post-RT and CT using self-assessment systems.

For HSCT patients, the evidence also favours follow-up; three good-[59,65,66] and seven adequate-quality studies[7,23,31,39,50,58,74] continued OM assessment between 18–28 days following transplantation. A further 12 studies, all of good or adequate-quality[12,22,25,30-32,42,43,57,69,72,75] specified follow-up OM assessments between 14 and 31 days.

Few papers mentioned any follow-up after 28 days for inpatients, so it is unclear how patients who continued to show signs of OM were monitored. Studies are required to assess the risks of discharging patients with OM, the effect OM has on the patient's quality of life (QoL) and what level of follow-up is appropriate. These questions must be addressed before the importance of long-term monitoring of OM can be determined.

Recommendation 6: *inclusion of patient-reported outcomes*

6A – Patient-reported outcomes, for pain at the very least, should be included in all OM assessments.
Evidence: sufficient/strong, therefore strongly recommended.

6B – Assessment of subjective measures should happen prior to any physical examination (including self-examination) of the mouth.
Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 6: inclusion of patient-reported outcomes
Thirty-three[12,23,24,26-29,31-35,37-40,43,46,49-53,58,60,61,63-65,69,71,73] out of 57 papers supported the use of patient-reported outcomes for each OM assessment, whereas 11 papers [21,22,25,34,36,48,54,57,70,74,75] provided evidence that they were unnecessary.
The degree of patient involvement varied considerably. In the studies using the NCI-CTC and WHO scales ($n = 22$), minimal self-assessment requires patients to indicate presence or absence of pain only, but the majority of these studies were supplemented with a more comprehensive self-assessment. Nine studies out of the 33 used a visual analogue scale (VAS)[12,23,24,29,32,40,61,64,69] and four studies[28,50-52] used longer patient questionnaires.
Changes in subjective measures of OM, e.g. pain, can precede changes in objective examinations.[35] Furthermore, studies by Cella and Sonis and their respective colleagues show that patient-reported measures of OM correlated closely with clinical measures[28,64]. Self-assessment may therefore allow healthcare teams to implement preventative or palliative interventions at an early stage, which may help to reduce the peak severity and/or duration of OM. The taskforce recommends that patient self-reported outcomes should be included with OM assessments. Due to the pain involved in physical examination, the taskforce is of the opinion that self-assessments are best made prior to examination.[64]

Recommendation 7: *pain scoring*

The use of pain scoring, and VAS tools in particular, should be used at each routine assessment.
Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 7: pain scoring
Subjective assessments of pain are included in the majority of scales, but are often limited to the question 'Do you have pain?' without any indication of severity. For this

analysis, pain scoring is taken to be pain assessments that use either a VAS or scales that grade different intensities of pain according to specific descriptors, such as the Brief Pain Inventory.

Pain scoring was reported in six good-quality[40,52,61,64-66] and 18 adequate-quality studies[12,23,24,28,29,31-33,37,39,46,50,53,60,69,71,73]. In four studies, pain scoring was added to instruments that did not include pain assessments[23,50,51,61]. Nine studies using the WHO or NCI-CTC scales[24,28,29,32,43,52,60] added scoring, even though a yes/no measure of pain is integral to these scales.

There is now sufficient evidence that patient-reported outcomes for pain should be included in assessments (see Recommendation 6). It is the opinion of the taskforce that pain scores relate to changes in the oral mucosa and provide an indication of the course of OM and the effectiveness of interventions over time. In particular, a VAS is simple to use by patients and also easy to analyse by healthcare teams[40].

Recommendation 8: *objective, subjective and functional measures of OM*

8A – OM assessments should use instruments or a combination of suitable scales containing elements covering physical changes in the oral mucosa, functional changes and subjective changes.

Evidence: strong, therefore strongly recommended.

8B – Where a selected instrument lacks one or more of these categories, a combination of scales should be adopted. The taskforce favours the combination of physical and functional grading and a VAS for patient pain and other subjective factors.

Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 8: objective, subjective and functional measures of OM

There is strong evidence (eight good-quality studies)[35,40,52,54,61,64-66] and 39 adequate-quality studies[7,12,21-26,28-34,37,39,41-44,46,48-51,55-58,60,62,68,69,71-75] that the oral cavity should be examined to assess physical (objective) changes, using a good light source. Only one study graded OM purely on patient-reported pain, with no physical assessment[53].

In terms of functional changes (swallowing, voice and chewing), 41 studies supported their use in assessment[21-24,26-29,31-41,43-46,49,51-53,55,57,60,62,64-72,75]. There was also strong evidence to support the assessment of subjective measures of OM (pain, dryness and sensitivity); only eight studies did not include any subjective measure at all[7,25,14,42,48,54,59,74].

The evidence for combining tools was mixed, with 22 supporting [23,24,28,29,31-33,35,38,39,43,50-53,55,60,61,65,69,71,73] and 35 not supporting[7,12,21,22,25-27,30,34,36,37,40-42,44-49,54,56-59,62-64,66-68,70,72,74,75] a combination. In the studies that support a combination of assessment tools, most of them added a patient self-assessment element, often a VAS. It is the opinion of the taskforce that where OM assessments lack functional and/or subjective measures, patient-repor-

ted assessments should be added to the routine assessment procedure. The MASCC guidelines highlight that objective, subjective and functional measures should be clearly differentiated in scales[10,83].

Recommendation 9: *validity and reliability of tools*

Validated assessment instruments should be used. If tools are modified, or new scales are employed, they should be fully validated. Inter-rater reliability should be tested regularly.

Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 9: validity and reliability of tools

The evidence for using validated tools was taken from studies that included a discussion of these issues, tested the tool's validity or referenced an original paper that validated the tool in question. A high proportion of papers (n = 38) did not mention validity in any of these ways, including four studies that used their own assessment scales[27,29,43,74]. It is worth noting that the widely-used WHO scale has never undergone rigorous validation tests; its use is based upon the opinion of experts and nearly 30 years of accumulated experience.

Several studies used scales developed for different settings or contexts, for example, the use of OMI to assess OM in leukaemia rather than HSCT patients[51]. These findings raise the question whether investigators consider the appropriateness and limitations of particular instruments, or whether they choose a scale based on their own experience and expertise. In practice, it is likely that clinicians favour familiar instruments or scales that staff find easy to learn.

Five good-quality studies[52,54,61,64,65] and 12 adequate-quality studies[12,23,31,34,37,44,50,51,55,58,62,71] referred to the reliability of the tool, however, 39 studies did not consider reliability at all. In these cases, reliability may have been presumed by the authors, especially for the widely accepted tools.

In clinical practice, the taskforce recommends that reliability should be regularly monitored. Whilst this testing may not be strictly necessary for tools of proven reliability, it ensures that OM monitoring remains consistent between personnel and highlights when training courses on OM assessment are required.

Recommendation 10: *ease of use and patient comfort*

Assessments should be easy to use by the clinician and be comfortable for the patient. Any physical examination of the oral cavity should take the minimum amount of time and be a minimally invasive procedure.

Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 10: ease of use and patient comfort

Assessment of the oral cavity can be an uncomfortable experience for the patient; it is intrusive and many patients feel self-conscious about having their mouths examined. The examination itself may be painful and there is a risk of bleeding.

A total of eight studies (two good-quality,[54,64] six adequate-quality[12,30,39,49,50,71]) included discussions on ease of use and duration of assessment, but no studies specifically addressed these issues. There was also a lack of focus on patient comfort during assessment, which may reflect the investigative nature of the papers.

The WCCNR tool and the Oral Mucositis Nursing Instrument (OMNI) were found to be ideal for use in busy clinical practice, as they were quick and easy to use[12,54] Similar observations were made regarding the OMAS tool[1].

Excessive touching of the sensitive oral mucosa could induce greater damage and worsen its condition. For this reason, the taskforce is of the opinion that physical exams should take the least amount of time, be minimally invasive but precise. The taskforce recommends that scales with extensive oral examination by trained personnel, such as the MacDibbs and OMI scales should only be used after careful consideration and elimination of all other alternatives.

Recommendation 11: *training*

Clinicians assessing patients should be specifically trained in the application of the scale. Periodic inter-rater reliability should be used to monitor the need for staff training.

Evidence: insufficient, supplemented by expert opinion, therefore recommended based on expert opinion.

Commentary on recommendation 11: training

For the purposes of these guidelines, where the investigators were described as experienced, or calibration procedures or inter-rater reliability tests were used, the studies were considered to have included training. A total of 22 studies mentioned formal training of assessors[12,23,31,33-38,43,50-54,58,64,65,69,71,74,75].

The taskforce recommends that examiners should be familiar and proficient in using the assessment tool in question. Several papers describe structured training such as the use of photographs to help maintain assessment standards[23,31,61,71]. The consistency and reliability of the tester and method should be monitored at regular intervals to determine the need for training and retraining amongst staff[84]. The PSMA programme[34,36,37], effectively trains patients as well as staff. It is the opinion of the taskforce thorough training, as outlined in these studies, should be more widely adopted.

Summary

Table 3 shows a summary of the recommendations. The taskforce believes that this analysis points to some general principles for selecting OM assessment instruments.

Table 3: *Summary of recommendations*

Recommendation	**No.**
Strongly recommended	
OM should be assessed using a standardised protocol	1
OM assessments should continue after the end treatment until OM is fully resolved or the trend to resolution is established	5
Patient-reported outcomes should be included in all OM assessments	6A
OM assessments should use instruments or a combination of suitable scales containing elements covering physical changes in the oral mucosa, functional changes and subjective changes	8A
Recommended	
Routine assessments should take place	2
Patient self-reporting should form an integrated part of the assessment	
Frequent assessment of OM is recommended throughout the course of any therapy, especially for patients who are most at risk of developing OM	4A
Recommended based on expert opinion	
A comprehensive baseline oral assessment should be made prior to treatment, where OM is expected	3
A further baseline assessment of OM should be taken as close to the administration of the first treatment dose as possible	4B
Assessment for all patients should take place on a daily basis during the period when OM is likely to first occur, or be at its peak	
Depending on the severity of baseline OM assessments and risk factors,assessments will need to continue at regular intervals (daily, every 2–3 days, weekly) as OM resolves	
Assessment of subjective measures should happen prior to any physical examination (including self-examination) of the mouth	6B
The use of pain scoring, in relation to changes in the oral cavity,should form part of OM assessment	7
Where a selected instrument lacks one or more of these categories a combination of scales should be adopted	8B
Either validated assessment instruments should be used, or if tools are modified or new scales are to be employed they should be fully validated	9
Inter-rater reliability should be tested on a regular basis	
Assessments should be easy to use by the clinician and to be comfortable for the patient. Any physical examination should take the minimum amount of time and be a minimally invasive procedure	10
Clinicians assessing patients should be specifically trained in the application of the scale. Periodic inter-rater reliability should be used to monitor the need for staff training	11

Abbreviation: OM, oral mucositis.

In the out-patient setting emphasis should be placed on patient self-evaluation. The PSMA programme demonstrates that patients are capable of clinically-relevant assessments which can be verified by a healthcare professional during patients' visits to clinic. In the in-patient setting where the burden of assessment falls on nursing staff, instruments should be quick and easy to implement while clinically effective. This analysis points to simple-to-use scales such as the WHO scale or the OAG, coupled with a VAS for pain. However, several instruments have been developed more recently and the taskforce calls for more studies into their clinical application (preferably head-to-head with the WHO and OAG).

The choice of instrument for the assessment of OM in the research setting requires careful consideration; investigators must ensure that the instrument covers all elements of OM relevant to the study. The recommendations represent a consensus based on an interpretation of the recent literature identified in an extensive literature review, and the expert experience of the OMAG taskforce. Any clinician using these guidelines is expected to use their own experience to determine appropriate care for their patients.

Appendix 1.

Questions considered pertinent to OM assessment, defined prospectively by the taskforce

Question no.	Question text
Question 1.1	Is a standardised procedure used?
Question 1.2	What elements are included in the procedure?
Question 2	Is there evidence to suggest that routine assessment can affect:
	a. the management of OM?
	b. healthcare team reported outcomes?
	c. patient reported outcomes?
Question 3.1	In an inpatient setting, is there evidence to support an OM assessment:
	a. prior to initiating treatment?
	b. during treatment?
	c. post-treatment?
Question 3.2	Was the OM assessment sufficient to meet study goals?
Question 4.1	In an outpatient setting, is there evidence to support an OM assessment:
	a. prior to initiating treatment?
	b. during treatment?
	c. post-treatment?
Question 4.2	Was the OM assessment sufficient to meet study goals?
Question 5.1	How often was an OM assessment carried out?
	a. less than one daily?
	b. once daily?
	c. more than once daily?
Question 5.2	Is there evidence that this frequency was sufficient to meet study goals?
Question 6	Is there evidence to support patient reported outcomes (subjective assessment) in the assessment procedure?
	a. before oral cavity examination?
	b. with each assessment?
	c. not at all?
Question 7	Is there evidence to suggest that the patient's oral intake was taken into account during assessment?
Question 8.1	Is there evidence to suggest that the patient's pain score was taken into account during assessment?

Question no.	Question text
Question 8.2	Was the pain score self reported,or reported by a healthcare professional?
Question 9	Is there support for examination of the oral cavity for the following:
	a. objective changes (e.g. erythema, lesions, oedema)?
	b. subjective changes (e.g. pain, sensitivity, dryness)?
	c. functional changes (e.g. voice, swallowing, chewing)?
Question 10.1	Is there evidence to support one assessment scale over another?
Question 10.2	Is there evidence to support a combination of assessment tools?
Question 11	When deciding which tool to use, does the paper refer to the following factors:
	a. validity?
	b. reliability?
	c. ease of use for the healthcare clinician?
	d. time taken to use the tool?
	e. comfort for the patient?
Question 12	Was training given to the assessors prior to use of an assessment tool in OM?

Abbreviation: OM, oral mucositis.

Appendix 2.
Literature search terms

Published papers

An electronic search of the Cochrane library and Medline and Embase databases used the following search terms:

'Oral mucositis' OR oromucositis OR ('mucosal cells' AND (mouth OR oral)) OR 'Stomatitis' [MeSH] OR stomatitis

AND

(('Radiotherapy' [MeSH] OR 'CT, Adjuvant' [MeSH]) OR radiotherapy OR chemotherapy OR 'Bone Marrow Transplation' [MeSH] OR 'Bone Marrow Transplantation' OR 'Bone Marrow Transpl' OR 'Bone Marrow Transplants' OR 'Stem Cell Transplantation' [MeSH] OR 'Stem Cell Transplantation' OR 'Stem Cell Transplant' OR 'Stem Cell Transplants')

AND

(assessment OR examination)

Limits: All Adult: 19+ years, Publication Date from 1989/12/31, English, Humans. All the MeSH terms were exploded to capture anything that appealed below the term in the hierarchy and free text terms were used to ensure that all the relevant information was found.

Abstracts

Where available online at time of searching, abstracts from the following conferences were searched from 2003 to 2005: ASH (2005 only available), ESMO (2004), ECCO (2005 only available), ASCO (2003–2005) and EBMT (2003–2005). Conference websites were searched with specific combinations of the following keywords:

- Oral mucositis AND assessment OR examination OR stomatitis OR radiotherapy OR chemotherapy OR bone marrow transplantation OR bone marrow transplant OR bone marrow transplants OR stem cell transplantation OR stem cell transplant OR stem cell transplants.
- Stomatitis AND assessment OR examination OR stomatitis OR radiotherapy OR chemotherapy OR bone marrow transplantation OR bone marrow transplant OR bone marrow transplants OR stem cell transplantation OR stem cell transplant OR stem cell transplants.
- Mucosal AND assessment OR examination OR stomatitis OR radiotherapy OR chemotherapy OR bone marrow transplantation OR bone marrow transplant OR bone marrow transplants OR stem cell transplantation OR stem cell transplant OR stem cell transplants.

Identified abstracts were examined and those where OM was not a primary endpoint were discarded. For abstracts in which OM was a primary endpoint, the abstract was compared against papers already identified in the electronic literature search and against papers recently published through PubMed using the following combination of keywords: Author initial AND (Mucositis OR stomatitis). If the data were not published, the first author of the abstract will be contacted to see if the paper is 'in press'.

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Chapter 7

The effectiveness of commonly used mouthwashes for the prevention of chemotherapy-induced oral mucositis: a systematic review

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Abstract

Daily chlorhexidine mouthwash is often recommended for preventing chemotherapy-induced oral mucositis. Povidone-iodine, NaCl 0.9%, water salt soda solution and chamomile mouthwash are also recommended. However, the effectiveness of these mouthwashes is unclear. Therefore, we performed a systematic review to assess the effectiveness of mouthwashes in preventing and ameliorating chemotherapy-induced oral mucositis. Based on study quality, three out of five randomized controlled trials were included in a meta-analysis. The results failed to detect any beneficial effects of chlorhexidine as compared with sterile water, or NaCl 0.9%. Patients complained about negative side-effects of chlorhexidine, including teeth discoloration and alteration of taste in two of the five studies on chlorhexidine. The severity of oral mucositis was shown to be reduced by 30% using a povidone-iodine mouthwash as compared with sterile water in a single randomized controlled trial. These results do not support the use of chlorhexidine mouthwash to prevent oral mucositis.

Introduction

Oral mucositis occurs in about 40% of patients who undergo cytostatic chemotherapy for malignancies[1, 2]. Virtually every patient who has undergone myeloablative therapy to prepare for a haematopoietic stem cell transplant (HSCT) develops mucositis, with 67% developing severe oral mucositis[3].

Damage to the mucous membranes (mucositis) can occur as a consequence of the direct effects of cytostatic drugs on the rapidly dividing cells in the tissues in the mouth. The initial symptoms of mucositis usually present between the fourth and seventh day after chemotherapy[4]. White discoloration of the mucous membranes mostly precedes the redness, oedema and lesions. These lesions can develop into large painful ulcers that can seriously hinder eating and drinking[5]. Furthermore, the protective effect of saliva can be reduced – due to a decrease in the quality and quantity – increasing the chance of developing infection[6, 7].

Severe mucositis results in a significant reduction in the quality of life, potential nutritional deficit and even the postponement of chemotherapy[8]. A recent study among 92 stem cell transplant recipients in eight centres in the United States, Canada and Europe demonstrated that the amount and severity of oral mucositis correlated with the number of days that patients required intravenous antibiotics, analgesics and parenteral feeding. The severity of mucositis among stem cell transplant recipients was also correlated with the number of admissions and readmissions, hospital costs and mortality[9].

The high incidence and severe consequences of mucositis among patients who undergo chemotherapy underline the importance of good prevention.

Rinsing the mouth daily with chlorhexidine solution is a preventive measure frequently recommended by nurses. Solutions of sodium bicarbonate, chamomile and 0.9% saline are also often used in the Netherlands[10]. The extent to which these mouthwashes actually help to prevent mucositis is unclear. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis have been produced[11], but only two studies were used as evidence to support the use of chlorhexidine although there are more studies available in the international literature. Moreover, there was no meta-analysis. There is also a review by Clarkson et al[12]. involving patients who received chemotherapy and/or radiotherapy. However, it is commonly known that mucositis induced by chemotherapy differs from that induced by radiation[11]. Therefore, we undertook to search the international literature afresh to ascertain whether these mouthwashes actually contribute to the prevention of oral mucositis among patients who undergo treatment with cytostatic chemotherapy.

Method

Search strategy

The Medline and Cinahl databases were searched for the relevant literature published from 1992 to the autumn of 2004. The search was restricted to these years in order to

obtain maximal validity in the light of oncology care today. The search terms 'mucositis, 'stomatitis' and 'chemotherapy' were used in combination with 'prevention', 'mouthwashes', 'antiseptic', 'oral infection', 'chlorhexidine', 'chamomile', 'PVP-iodine' and 'sodium bicarbonate'.

Selection criteria

All randomized studies of the effect of mouthwashes for the prevention and amelioration of oral mucositis in adult patients undergoing chemotherapy were eligible for this systematic literature study. Two independent assessors CP and RU selected the articles. The titles and/or abstracts were used to identify those that meet the inclusion criteria. Studies were selected if they involved using mouthwashes for oral mucositis, had a controlled study design, involved adult patients with cancer who received chemotherapy and included an outcome measure of the severity of mucositis. If a difference of opinion arose, a third author was consulted before the article was included or excluded.

Study quality and analysis

The quality of a systematic review is related to the quality of the studies used with randomized controlled trials topping the hierarchy of evidence[13]. Quality assessment allows appraisal of the studies included and also aids data synthesis. The quality of studies was assessed for randomization, blinding and the intention-to-treat analysis. In randomized controlled trials, patients are randomly assigned to either a control or an experimental group. For blinding, a trial was classified as adequate if it was described as 'double-blind', a type of clinical trial in which neither the subject nor the investigator knows what treatment the patient is receiving. An intention-to-treat analysis specifies how to handle non-compliant patients in a randomized controlled trial. This analysis requires that patients be analysed in the groups into which they were randomized, regardless of whether or not they complied with the treatment allocated[14].

In a meta-analysis or statistical pooling, the data gathered in the framework of a systematic review are statistically combined to estimate the effect of the intervention studied in the research[15].

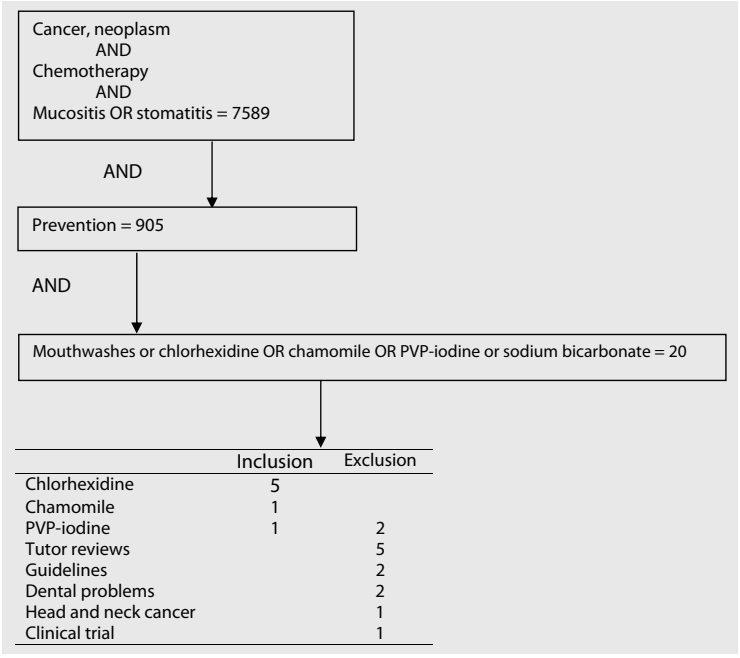
The findings of the individual studies were analysed in a meta-analysis using the software Review Manager 4.2[16]. In systematic reviews, homogeneity refers to the degree to which the results of studies included in a review are similar. A fixed effect model was allowed since homogeneity was found between the studies (Chi-squared test: $P < 0.1$).

This is a statistical model that stipulates that the units under analysis (people in a trial or study in a meta-analysis) are the ones of interest, and thus constitutes the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model. Variation between the estimates of effect from each study (heterogeneity) does not effect the confidence interval in a fixed effect model.

Results

The search term 'mucositis or stomatitis' provided 7589 hits using Medline and Cinahl for the period 1992–2004. When combined with 'prevention', there were still 905 articles. After combining with 'mouthwashes', 'antiseptic', 'oral infection', 'chlorhexidine', 'chamomile', 'PVP-iodine' or 'sodium bicarbonate', 20 articles remained (Fig. 1). Five of these studies investigated chlorhexidine in a randomized controlled clinical trial (RCT)[17-21]. Three articles were found which investigated iodine solution as a mouthwash. However, further investigation revealed that these three articles were all reports of the same study. Hence only the most complete one is included in the review[22].
One study determined the effects of chamomile solution[23]. The other 11 articles were excluded: five were not RCTs but tutor reviews, two investigated dental problems and two discussed guidelines for mucositis and were therefore excluded. One study investigated micronized sucralfate versus salt and soda mouthwashes in head and neck cancer patients who received radiation therapy. This study was excluded because it dealt with radiation-induced mucositis and not chemotherapy-induced mucositis. Another study also investigated sodium bicarbonate, but did not use a randomized study design (clinical trial) and was therefore excluded.
No RCTs investigating sodium bicarbonate were found. However, three articles were found which investigated salt and soda, this solution is similar to sodium bicarbonate. In one study, where chlorhexidine was used as the intervention, the control group used a water, salt and soda solution. This study was included[20].

Figure 1: *Selection of articles*



	Inclusion	Exclusion
Chlorhexidine	5	
Chamomile	1	
PVP-iodine	1	
Tutor reviews		2
Guidelines		5
Dental problems		2
Head and neck cancer		2
Clinical trial		1
		1

Study characteristic

The seven studies (Tables 1 and 2) included data from 863 adults with cancer with a mean age of 53.6, 72% of the patients in the studies received chemotherapy, only 6% of the patients received HSCT, for 22% of the patients it is unknown which treatment was received. The World Health Organization instrument[24] was used to score mucositis in three studies[21-23]: one study adapted this scale[18], two studies[19, 20] used the Oral Assessment Guide[25] and one study employed a four-point scale developed by the investigator[17]. The frequency of assessing mucositis varied from once to twice a day, once weekly, and on three separate occasions during treatment.

Table 2: *Overview of the effect of mouthwashes other than chlorhexidine in preventing mucositis among patients undergoing chemotherapy*

Author / date	Intervention	Dose	Control group	Number of patients +	Effect in terms of preventing mucositis	Side effects	Successful randomization / blinding / Intention-to-treat analysis
Fidler/ 1996	20 drops chamomile solution in 100 ml water	3x daily 1 min rinse 3 to 5x	Mouthwash without chamomile	Intervention group: 82 Control group: 82 Power ≤ 80	Mucositis score * Physician: intv. 40% cont 45% Patient intv. 49% cont. 61%	Chamomile was well tolerated with no increase in nausea and vomiting	Yes / Complete / Yes
Adamietz/ 1998	PVP-iodine betaisodona®	3 min. rinse 4x daily	Sterile water	Intervention group: 20 Control group: 20 Power ≤ 80	Mucositis score * Intv. 70% Cont. 100%	None: as long as the iodine was not swallowed as then there is a risk of hyperthyroidism	Yes / no, open/ Yes

+ Power calculation assuming α = 0.05, Δ = 20% in frequencies or 20% of scale range
* WHO scale ** Oral Assessment Guide (OAG)

Study quality

All studies randomly allocated subjects to either an intervention or a comparison group. Only one study assigned patients to one of the treatment groups by stratified block randomization[21], the blocks being selected using a set of random sampling numbers. A double-blind study design was used in five studies, though the group assignment was revealed in one study at an early stage[18]. Another study had an open study design[22] and the last study did not report blinding at all[17]. The analysis was conducted on an intention-to-treat basis in four studies[17, 21-23].

Compliance

The compliance of patients with treatment has an important effect on the results of different studies, and is therefore an important element to consider[26]. However, patient compliance was assessed in only three studies. Dodd et al.[20] collected the mouth rinse bottles and measured the amounts remaining and compared this with what should have been used. Compliance in this study was very high (92%), although it is not known if patients disposed of their mouth rinses in another manner, but the investigators had no reason to believe that this occurred. However, Epstein et al.[17] found less positive results regarding compliance with rinsing. In their study, assessment of compliance was based on medication records and on an interview at weekly assessment visits. Patients assigned to rinsing with Nystatin alone or in combination with chlorhexidine showed poor compliance, with only 47% of patients in the nystatin-chlorhexidine rinse group

Table 1: Overview of randomized studies into the effect of chlorhexidine as a mouthwash for preventing mucositis in patients undergoing chemotherapy

Author / Year	Intervention	Dose	Control group	Number of Patients +	Effect in terms of preventing mucositis	Side effects	Successful randomization / blinding / Intention-to-treat analysis
Epstein/ 1992	Group 1. chlorhexidine 0.2% Group 2. nystatin solution 100,000 U/ml. Group 3. chlorhexidine + nystatin solution	4x daily 1 min rinse with 15ml for all groups	Salt solution	Group 1: 18 Group 2: 16 Group 3: 34 Control group: 18 Power ≤ 80	Max mucositis * 1: mean 3.53 2: mean 3.45 3: mean 3.95 c: mean 2.46	Not stated	Yes / Unknown / Yes
Rutkauskas/ 1993	Chlorhexidine 0.12%	2x daily 30 sec. rinse with 15 ml	Mouthwash without chlorhexidine	Intervention group:10 Control group: 11	None** (no numbers stated in the publication)	Brown discolouration of the teeth and altered taste in chlorhexidine group. Number and severity not stated.	Yes / not complete / No Unblended early Excluded patients n=8 did not tolerate mouth inspection.
Dodd/ 1996	Chlorhexidine 0.12%	2x daily 20 sec. rinse with 20 ml	Sterile water	Intervention group: 112 Control group: 110 Power > 80	Mucositis **** present/severity: Intv. 28%/ mean 14.10 cont. 26%/ mean 13.79	Not stated	Yes / Complete / No 51 patients dropped from the study. Discontinued, death, month wash taste unpleasant
Dodd/ 2000	Group 1. 1 teaspoon salt + 1 teaspoon soda in 454 ml water Group 2. Chlorhexidine 0.12% Group 3. Magic =5 ml lidocaine solution (0.5%) + 0.25 ml diphenhydramine hydrochloride + 14.75 ml aluminium hydroxide	4x daily 20 sec. rinse with 20 ml	None	Group 1: 48 Group 2: 51 Group 3: 42 Power > 80	Severity mucositis ***** 1: mean. 13.21 2: mean. 13.71 3: mean. 13.81	Unpleasant feeling in the chlorhexidine group Number not stated	Yes / Complete / No Excluded patients n=58 Too ill, too painful, nauseous, groups remained comparable
Pitten/ 2003	Chlorhexidine 0.3% (Skinsept mucosa®)	3x daily 30sec. rinse with 20ml	Amine-stannous fluoride (Meridol®)	Intervention group: 24 Control group: 23 Power ≤ 80	Severe mucositis*** Odds ratio 6.3 (1.02-49.67)	Uncomfortable or painful	Yes (block randomized)/ Complete/Yes

+ Power calculation assuming α = 0.05, Δ = 20% in frequencies or 20% of scale range

* Four-point scale developed for this study ** Adapted WHO 4 – point scale *** WHO scale **** Oral Assessment Guide (OAG)

using the rinse a 100% of the time, 78% of patients using chlorhexidine at all times, but 89% of them using the saline solution group at all times.
Pitten et al.[21] used brown glass bottles. On visiting the patients to assess mucositis, the clinician checked if the volume remaining in the bottle correlated with the number of rinses. The findings indicated that the patients had rinsed properly.

Chlorhexidine
Chlorhexidine is approved for use as an antibacterial mouthwash at a concentration of 0.12% and 0.2% to prevent the build-up of dental plaque and to prevent gingivitis[27]. Its broad spectrum of antibacterial activity, minimal systemic absorption and ability to bind to oral surfaces led to use as prophylaxis in an attempt to prevent the development of oral mucositis[28].
Chlorhexidine has been tested in five randomized studies for its effects in preventing oral mucositis in patients undergoing chemotherapy (Table 1).
Epstein et al.[17] investigated three different mouthwashes, chlorhexidine, nystatin and a combination of nystatin-chlorhexidine and compared these with rinsing using a saline solution. All patients (*n*=86) who received medical therapy that resulted in severe neutropenia were included into the study. Fifty-six patients (65%) received aggressive chemotherapy for remission induction or consolidation. Thirty patients (35%) received HSCT. The patients were asked to rinse with the mouthwash after eating. Oral hygiene was assessed using the gingival index and plaque levels, and mucositis was assessed using a four-point scale specially developed for the study. Bacterial and fungal oral cultures were done on a weekly basis. There was no difference in mucositis between the four groups although bacterial and fungal infections were found less often among the patients using chlorhexidine.
Rutkauskas and Davis[18] investigated the effect of chlorhexidine versus a placebo in patients undergoing HSCT or remission-indication chemotherapy. The study showed chlorhexidine to be ineffective in preventing mucositis. Unfortunately, the data were also presented in a form that made it impossible to include them in the meta-analysis.
Dodd et al.[19] investigated the effect of an instruction programme for the systematic oral care of 222 patients undergoing chemotherapy provided by nurses in combination with two mouthwashes (chlorhexidine and sterile water). The preventative effects of rinsing with chlorhexidine were no greater than those of rinsing with sterile water leading the investigators to recommend rinsing with water only.
Dodd et al.[20] also compared the preventative effects of three mouthwashes (chlorhexidine, salt and soda in water) and 'magic mouthwash' (containing Lidocaine, Benadryl and Maalox) in patients who received stomatotoxic chemotherapy at home and were monitored on an outpatient basis. Nurses used the Oral Assessment Guide for initial assessment, instructed patients on how to assess their own mouths, then phoned the patients every other day to note their oral status. No differences in the severity of mucositis were found between the three groups nor were there any significant differences in the time taken for signs and symptoms of mucositis to subside. The first signs of mucositis were seen within 6.6 days in the chlorhexidine group, within 7.0 days in the water/salt/soda group and within 7.2 days in the 'magic mouthwash' group.

Pitten et al.[21] investigated chlorhexidine versus amine-stannous fluoride solution to investigate whether leucopenic patients who cannot clean their teeth mechanically might have clinical benefit from an antiseptic mouth rinse containing chlorhexidine. The statistical analysis showed that there was a significant decrease in the numbers of micro-organisms in the oral cavity during leucopenia among those in the chlorhexidine group compared with that in the control group. However, this did not translate into any measurable clinical benefit. Patients rinsing with chlorhexidine also indicated that the rinsing was unpleasant and even painful.

Power

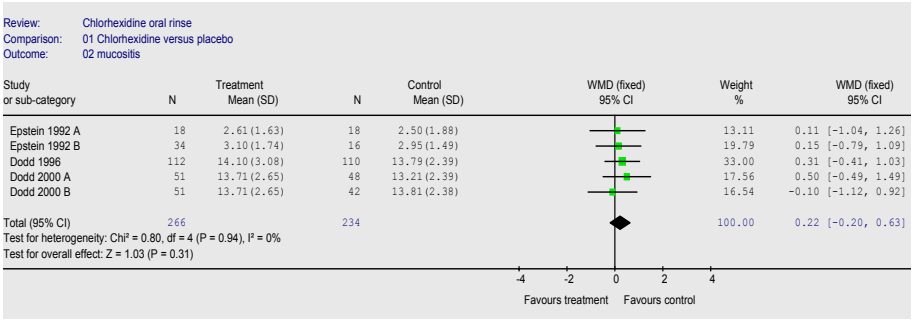
None of the studies reported a power calculation, so we calculated this from the numbers of patients reported, assuming an alpha of 0.05 (two-sided) and a clinically relevant effect size of 20% of the scale range for severity of mucositis in several studies, or a 20% difference in frequencies in studies with presence or absence of mucositis as the main outcome. Only the studies by Dodd et al.[19, 20] had sufficient power (≥ 80%). The study by Fidler et a[23] had an estimated power of 70%, whereas the power of the other studies was less.

Meta-analysis

Within the meta-analysis, the results from individual studies were weighted in inverse proportion to their variance, resulting in a weight proportional to the size of the studies. Four out of five studies that investigated chlorhexidine mouthwash for preventing mucositis were eligible for inclusion in the meta-analysis. Rutkauskas and Davis and Pitten et al.[18, 21] did not state all of the necessary figures for this. The study by Epstein et al.[17] had a total of four groups and in the analysis was approached as two studies, namely chlorhexidine versus saline solution and chlorhexidine nystatin versus nystatin.

The study by Dodd et al.[20] was also entered as two studies (chlorhexidine vs. water/salt/soda and chlorhexidine vs. 'magic mouthwash'). All the information is contained within the forest plot graphical representation of the results in Figure 2.

Figure 2: *Forest plot mucositis*



Taken together the results, the five studies showed no significant effect of chlorhexidine mouthwash (Weighted mean differences 0.22; 95% confidence interval =–0.20,

0.63). The test for heterogeneity and the test for overall effect are given at the bottom of the forest plot. It is important to remember that heterogeneity may be present when all or most studies indicate the same treatment effect, but the size of the effect differs or the trials are contradictory about the effect[29]. The results are considered homogenous when the effect sizes differ due to sampling errors.

Other mouthwashes

Table 2 provides an overview of randomized studies into the effect of mouthwashes other than chlorhexidine in preventing mucositis in patients undergoing chemotherapy.

Fidler et al.[23] evaluated the effect of a chamomile solution in a group with a total of 164 patients treated with 5-FU chemotherapy. After randomization, 82 patients received a mouthwash with a chamomile solution and 82 patients received a mouthwash without. All patients received oral cryotherapy for 30 min with each dose of 5-FU. Mucositis was scored by the physician (scale of 0–4). The patient also recorded his or her score on a daily basis. No differences were found between the chamomile group and the control group in either the incidence or severity of mucositis.

Adamietz et al.[22] investigated the preventative effects of iodine solution as a mouthwash compared with rinsing with water in 40 patients given radiochemotherapy (n=20 for both groups). The World Health Organization criteria for mucositis (scale of 0–4) were used to estimate the severity and duration of the mucositis. The iodine group had a significantly less severe mucositis compared with the control group and the duration of the mucositis was shorter (2.8 weeks for the iodine group vs. 9.3 weeks for the control group). However, the study was too small to be confident that the difference observed was not simply a chance finding.

Conclusion

A systematic review was used to assemble and synthesize the evidence for the effect of commonly used mouthwashes on the prevention of chemotherapy-induced oral mucositis. Comprehensive search methods were used to minimize any bias.

With the exception of iodine solution, none of the studies investigated were able to demonstrate an effect in preventing mucositis in patients undergoing chemotherapy.

Chlorhexidine

Chlorhexidine is widely used and has been investigated albeit in various small studies. Individually, the studies found chlorhexidine to be ineffective and increasing power through meta-analysis did not alter this. Studies done before 1992 found a positive effect of rinsing with chlorhexidine[30-32] whereas those conducted in the period 1992–2004 found either no effect or a negative effect. One possible explanation could be that bacterial infections were better controlled and managed after 1992 than before because of better antibiotics.

The discoloration of teeth, the bitter taste and the unpleasant sensation experienced

together with ineffectiveness are sufficient reasons for recommending sterile water, 0.9% saline solution or sodium bicarbonate (water, salt and soda) rather than chlorhexidine. Furthermore, these alternatives are less expensive and readily available in everyday nursing practice.

Other mouthwashes

Most of the other formulations had no effect on the prevention of mucositis. The antifungal drug nystatin, even in combination with chlorhexidine, was no exception[17].

Even chamomile, which has an anti-inflammatory effect, proved ineffective[33].

One study did demonstrate that iodine solution was effective as a mouthwash, but this finding must be treated with caution, due to the small sample sizes involved. Moreover, side-effects were not reported, though, when accidentally swallowed, iodine can cause hyperthyroidism.

The sample sizes varied from 21 to 222 and none of the studies indicated the power calculation based on a proposed treatment effect even though adequate statistical power is crucial to minimize type-II or beta errors[34]. This shortcoming was compensated to some extent by the meta-analysis supporting the negative conclusions for chlorhexidine, which does not apply to other mouthwashes.

Patient compliance with the intervention has an important effect on the results and should always be considered[26], yet only three studies did so[17, 20, 21].

Based on our findings and those of others[11, 12], the use of chlorhexidine as well as other mouthwash for preventing oral mucositis in patients undergoing chemotherapy cannot be recommended. The use of an iodine solution could be promising, but should be investigated further.

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Chapter 8

Quality assessment of the methodology used in guidelines and systematic reviews on oral mucositis

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Abstract

The objective of this study was to identify and to assess the quality of evidence-based guidelines and systematic reviews. We used the case of oral mucositis to apply general quality criteria for the prevention and treatment of oral mucositis in patients receiving chemotherapy, radiotherapy or both.

Literature searches were carried out in several electronic databases and websites.

Publications were included if they concerned oral mucositis involving adults treated for cancer and had been published after January 1, 2000. As far as systematic reviews are concerned, the article had to report a search strategy, the search was minimally conducted in the databases PubMed or Medline and the articles included in the review were subjected to some kind of methodological assessment.

The Appraisal of Guidelines for Research and Education (AGREE) instrument was used to assess the quality of the guidelines and the Overview Quality Assessment Questionnaire (OQAQ) was used for the quality of systematic reviews.

Thirty one articles met the inclusion criteria of which eleven were guidelines and 20 were systematic reviews. Nine of the eleven guidelines did not explicitly describe how they identified, selected and summarised the available evidence. Reviews suffered from lack of clarity, for instance in performing a thorough literature search. The quality varied among the different guidelines and reviews.

Most guidelines and systematic reviews had serious methodological flaws.

There is a need to improve the methodological quality of guidelines and systematic reviews for the prevention and treatment of oral mucositis if they are to be used in clinical practice.

Introduction

Clinical guidelines are an important tool to provide effective and efficient care. They are 'systematically developed statements to assist practitioner decisions about appropriate health care for specific clinical circumstances'[1]. To ensure high quality, the guidelines should be based on the best available scientific evidence [2].

Existing guidelines and protocols seem mostly based on tradition, subjective observation and incomplete evidence. This results in uncertainty among nurses about which advice or treatment is the best for their patients. The development of an evidence-based guideline is essential for those taking care of patients. The development of such guidelines may promote uniformity of care both within a centre, as well as between centres and potentially increase the quality of care provided to patients. Clinicians use a variety of guidelines and protocols. These documents vary in the degree of detail and the evidence upon which these guidelines and protocols are based is unknown. Systematic reviews can aid in guideline development because they involve searching for, selecting, critically appraising and summarising the results of primary research. The more rigorous the review methods used and the higher the quality of the primary research that is synthesised, the more evidence-based the practice guideline is likely to be[3].

In recent years, the number of available clinical practice guidelines has rapidly increased. This recent increase in the production of clinical practice guidelines has been accompanied by growing concern about the variations in guideline recommendations and quality. In fact, several studies suggested that many existing guidelines are of poor quality[4, 5]. To see whether these concerns about the quality of existing guidelines and systematic reviews are justified, we undertook a study to examine the quality of guidelines and systematic reviews using guidelines and systematic reviews developed for the prevention and treatment of oral mucositis.

Oral mucositis is a burdensome and potentially dangerous side effect of many anticancer therapies that include chemotherapeutic agents or ionising radiation[6]. Oral mucositis plays a significant role in the physical and psychosocial aspects of patients undergoing cancer therapy and presents a larger problem than is currently recognised from a public health perspective.

Incidence as well as severity may vary from patient to patient and the likelihood of developing mucositis is dependent upon the cancer treatment. As the primary advocates for patients, nurses are central to recognising, preventing and managing oral mucositis to ameliorate its debilitating effects on patients. Nurses have three primary responsibilities in managing oral mucositis:

(1) effective assessment and monitoring of the oral cavity as well as symptoms;
(2) disease management focusing on ensuring that appropriate intervention is available to patients; and
(3) patient education[7].

A potential mechanism for improving outcomes in patients with oral mucositis would be to ensure that those patients are receiving evidence-based care.

Aims

The primary objective of the current study is to identify and assess the quality of available guidelines and systematic reviews for prevention and treatment of oral mucositis. Rather than focussing on their content, we critically reviewed the methods employed and documented in writing the reviews and guidelines.

Materials and Methods

Definitions

A systematic review uses a predefined, explicit methodology. The methods used include steps to minimise bias in all parts of the process: identifying relevant studies, selecting them for inclusion and collecting and combining their data. Studies should be sought regardless of their results[8].

Guidelines are systematically developed statements to assist clinician and patient decisions about appropriate health care specific clinical circumstances[1].

Search strategy

To identify the guidelines focused on prevention and treatment of oral mucositis, the websites of the main international institutions involved with prevention and treatment of cancer were explored as recommended by various authors[9-14]. Guidelines on the prevention and treatment of oral mucositis published from 2000 to May 2006 were identified and downloaded. In addition, four computerised databases: PubMed, CINAHL (Cumulative Index of Nursing and Allied Health Literature); PiCarta (OCLC PICA system consisting the Dutch Central Catalogue and Online Content) and INVERT (Index of the Dutch nursing journal literature) were searched. All relevant English and Dutch websites were searched with the keywords: guidelines, stomatitis, mucositis, oral care and mouth care.

Relevant systematic reviews were identified by searching 8 electronic databases of articles published from January 1, 2000 through May 31, 2006. These were: PubMed, Embase, CINAHL, PiCarta, INVERT, DARE, Cochrane Database of Systematic Reviews and Psychinfo. This publication time frame guaranteed data from systematic reviews conducted in the recent past. Where one review clearly updated a previous review, only the most recent publication was used. To identify additional relevant studies the Science Citation Index was used to search for studies that cited located relevant papers.

Search strategies for electronic databases were developed sequentially, starting with PubMed, as this was expected to yield the highest number of relevant papers. The review used a search strategy with Medical Subject Headings and text words (Box 1). Similar search strategies were made for the other databases. There were no language restrictions applied.

***Box 1:** Search strategy PubMed*

(Oral Hygiene"[MeSH] OR "Stomatitis"[MeSH] OR "oral mucositis"[All Fields] OR "mouth care"[All Fields]) AND ("Radiation Oncology"[MeSH] OR "Medical Oncology"[MeSH] OR "Hematologic Neoplasms"[MeSH] OR "Oncologic Nursing"[MeSH] OR "Neoplasms"[MeSH] OR "chemotherapy"[All Fields] OR "radiotherapy"[All Fields] OR "cancer patients"[All Fields]) AND (review[pt] OR "meta-analysis"[pt] OR "quantitative* overview*"[tw] OR "systematic* review*"[tw] OR "systematic* overview*"[tw] OR "methodologic* review*"[tw] OR "methodologic* overview*"[tw] OR "guideline"[pt] OR "practice guideline"[pt] OR "health planning guidelines"[mh] OR "consensus development conference"[pt] OR "consensus development conference, nih"[pt] OR "consensus development conferences"[mh] OR "consensus development conferences, nih"[mh] OR "guidelines"[mh] OR "practice guidelines"[mh] OR (consensus[ti] AND statement[ti])

Selection criteria

Two reviewers (CP and PM) conducted independently screening of relevant studies for inclusion. Disagreements were resolved by discussion with a third member of the team (TvA). The first level of screening using titles, publication years and abstracts, was to include papers only if they concerned oral mucositis involving adults treated for cancer and had been published after January 1, 2000 and were probably a guideline or a systematic review

The second level of screening was based on full text, with the same criteria as described above. As far as systematic reviews are concerned, publications were only included, according to our definition of a systematic review. The article reported: (1) a description of the search strategy (2) a minimal search in the databases PubMed or Medline and (3) the articles included in the review were subjected to some kind of methodological assessment.

Instruments to assess quality

Quality of guidelines was assessed with the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument since it is internationally recognised, rigorously developed and a validated instrument that compares well with other instruments designed for this purpose[15]. Three reviewers (CP, PM and TvA) rated each guideline. The AGREE instrument instructs the reviewer to make a judgement as to the quality of the guideline, taking each of the appraisal criteria into consideration. The 23-item AGREE instrument is divided into the following six domains (see Box2): scope and purpose (three items); stakeholder involvement (four items); rigor of development (seven items); clarity and presentation (four items); applicability (three items); and editorial independence (two items)[16]. Each item is rated on a 4-point scale ranging from 4 'Strongly Agree' to 1 'Strongly Disagree', with two midpoints: 3 'Agree' and 2 'Disagree'. The scale measures the extent to which a criterion (item) has been fulfilled. The score for each domain is

obtained by summing up all the scores of the individual items in a domain and then standardising as follows:

$$\frac{\text{obtained score - minimum possible score}}{\text{maximum possible score - minimum possible score}}$$

The maximum score for each domain would be the number of questions multiplied by the number of reviewers multiplied times 4 (*ie*, the score for strongly agree). The minimum possible score for a domain would be the number of questions multiplied times the number of reviewers multiplied times 1 (*ie*, the score for strongly disagree). The final component of the AGREE instrument involves a recommendation regarding the use of the guidelines in practice as following;

1. 'Strongly recommended,' if the guideline rated high on the majority of items and most domain scores were 60%, indicating that the guideline had a high overall quality and could be considered for use in practice without alterations;
2. 'Recommended' with provisos or alterations if the guideline rated high or low on a similar number of items and most domain scores were 30%–60%, indicating that the guideline had a moderate overall quality;
3. 'Would not recommend' if the guideline rated low on the majority of items and most domain scores were 30%, indicating that the guideline had a low overall quality and serious shortcomings and thus should not be recommended for use in practice; and finally,
4. 'Unsure' if the guideline did not give sufficient information to enable to assess its quality[17].

Quality of systematic reviews was assessed with The Overview Quality Assessment Questionnaire (OQAQ)[18]. This scale was selected because of its strong face validity and the availability of a published assessment of its construct validity. (see Box 3) The validity of the scale has been thoroughly tested and clearly validated using several different measures[19, 20]. This instrument includes nine items pertaining to individual aspects in the reporting of a systematic review (e.g., were the search methods used to find evidence on the primary question stated?). Each item is assessed using a three-point scale (i.e. no, partially/can't tell or yes). A final question elicits an overall scientific quality of the systematic review based on the previous items on a scale of 1-7, with 7 indicating superior quality and a score of ≥ 5 indicating that the study has only minimal or minor flaws[21]. 'The Review Appraisal Form' was applied to each review independently by 2 researchers and then judged by consensus.

Results

Availability and quality of guidelines and reviews

After removal of duplicates, a total of 493 citations were identified from the electronic

searches (Figure 1). Two reviewers screened the titles and abstracts for further review. It was decided that 165 (34%) of the citations were potentially relevant based on the predetermined inclusion criteria. After reading the full text, the reviewers came to a consensus that 34 of these met the criteria for selection.

Guidelines

Eleven of the 34 publications were guidelines. Six of the 11 guidelines were downloads from the Internet of which three were English and three were Dutch. The five remaining guidelines were publications in peer-reviewed journals. Each guideline was scored for each of the six domains of the AGREE-instrument, as shown in Table 2.
A first finding is that none of the guidelines were of good overall quality. None of the guidelines had scores >60% in all domains and none had a score between 30% and 60%, in all domains, indicating low overall quality for all guidelines according to the AGREE Instrument. Almost all the guidelines were considered poor in the domains 'applicability' and 'editorial independence'.

Table 2: *quality assessment guidelines*

Averaged AGREE scores by domain						
Author/year	Scope and Purpose	Stakeholder Involvement	Rigor of Development	Clarity and Presentation	Applicability	Editorial Independence
(CBO 2004)[28]	93	44	56	61	48	22
(Rubenstein *et al.* 2004a)[6]	59	39	56	61	22	72
(Stricker 2003)[29]	56	50	38	56	11	11
(Barasch *et al.* 2006)[30]	33	53	25	47	0	17
(The Royal College of Surgeans of England 2004)[31]	70	8	10	67	19	0
(Milligan et al. 2001)[32]	33	19	8	28	11	28
(Oncology Nursing Society 2001)[33]	26	14	16	47	15	6
(LWVOC 2001a)[34]	22	6	5	58	19	0
(West & Mitchell 2004)[35]	33	6	5	22	4	28
(LWVOC 2001b)[36]	19	11	3	53	11	0
(National Cancer Institute 2005[23]	7	0	5	8	0	7

Applicability evaluates the likely organisational, behavioural and cost implications of applying the guideline, whereas editorial independence addressed potential conflicts of interest in guideline developers (e.g. due to sponsoring by companies selling products within the guideline scope). Nine of the eleven guidelines did not explicitly describe how they identified, selected and summarised the available evidence. Most of the guidelines did not provide an explicit link between the recommendations and the supporting evidence.

Systematic reviews

Only 23 of the 154 reviews were original systematic reviews. One review was an overview of two other included systematic reviews and in two of the reviews oral mucositis was not the primary topic, hence they were excluded. A total of 20 systematic reviews remained in this study. Agreement was reached on the scoring of all component scores and the overall quality scores with the need for an additional independent reviewer in two cases, because two of the 20 reviews were written by co-authors involved in this review.

Reviews suffered from lack of clarity, for instance in performing a thorough literature search, avoiding bias in the inclusion of studies and properly referring to the quality of the included studies. Table 3 shows the systematic reviews and contains the quality score of the 20 identified reviews. Interventions for preventing oral mucositis were described in seven reviews, only one review was found describing interventions for treatment of oral mucositis. All reviews made formal assessment of methodological quality of included randomised studies and most had included trials that were not double blinded for the patient and assessor. None of the reviews excluded trials from analysis because of low quality through a small sample size. Most of the reviews were clear in what types of participants, intervention and outcome measures were included in the review. The total number of studies included in reviews ranged from 7-71 with a median of 25 studies per review. Four of the 20 reviews conducted a meta-analysis.

Discussion

For this study, guidelines and systematic reviews in the area of oral mucositis were used to assess their transparency and quality; however, the approach we used could be applied to any clinical topic.

This review shows that the quality of most of the guidelines and systematic reviews for prevention and treatment of oral mucositis was low. Although some guidelines seem to have been more rigorously developed than others, many methodological flaws were identified. The AGREE instrument for quality assessment was used in screening the guidelines. This questionnaire has been endorsed by the WHO and the European Commission. The AGREE Instrument is a generic and validated questionnaire to assess both the quality of reporting and the methodological quality of some aspects of recommendations. It provides an assessment of the predicted validity of a guideline, i.e. the likelihood that it will achieve its intended use. It does not investigate, however, the accuracy of the recommendations within a guideline, nor its impact on patients' outcomes[22]. This instrument was developed in 2003 before five of the eleven guidelines included in this study were developed. This suggests that provided that committees that are developing or updating guidelines use the AGREE recommendations, the quality of future guidelines will likely improve. In cases where no information was available on a certain topic, the AGREE instrument recommends the rating 'strongly disagree'. This method

Table 3: *Quality assessment systematic reviews*

Averaged QOQA scores by question										
Author/year	Search methods stated	Search comprehensive	Inclusion/ exclusion criteria	Bias selection studies	Validity	Validity criteria	Combine findings	Primary question	Conclusions	Quality rate*
Worthington et al 2006[37]	A	A	A	A	A	A	A	A	A	7
Worthington et al. 2004 [38]	A	A	A	A	A	A	A	A	A	7
Sutherland & Brouwman 2001 [39]	A	A	A	A	A	A	A	A	A	7
McGuire et al. 2006 [40]	A	A	B	B	B	A	A	A	A	6
Potting et al. 2003 [41]	A	A	A	B	B	A	B	A	A	6
Donnelly et al. 2003 [42])	A	B	A	A	A	B	B	A	B	5
Bensadon et al. 2006 [43]	A	A	C	C	B	B	B	B	B	4
Migliorati et al.. 2006 [44]	A	A	B	B	B	C	B	B	A	4
Lalla et al. 2006 [45]	A	A	C	C	B	B	C	B	B	3
Bultzingslowen et al. 2006 [46]	A	B	C	B	B	B	B	B	B	4
Gottschalck et al. 2003 [47]	A	A	C	C	B	B	C	C	B	4

Author/year	Search methods stated	Search comprehensive	Inclusion/ exclusion criteria	Bias selection studies	Validity	Validity criteria	Combine findings	Primary question	Conclusions	Quality rate*
Jansman et al. 2001 [48]	B	B	C	C	C	C	C	C	C	2
Kwong 2004[49]	B	C	C	C	C	C	C	C	C	1
Sonis et al. 2004 [50]	B	B	B	C	C	C	C	C	C	2
Hendricks 2003 [51]	C	A	C	C	C	C	C	C	C	1
Epstein et al. 2002 [52]	B	B	C	C	C	C	C	C	B	2
Shih et al.2002 [53]	C	B	C	C	C	C	C	C	C	1
Scully et al. 2004 [54]	B	B	C	C	C	C	C	C	C	1
Scully et al. 2004 [55]	B	B	C	C	C	C	C	C	C	1
Sharma et al. 2005 [56]	B	B	B	C	C	C	C	C	C	3

A= Yes B= Partially (Can't tell) C= No

* The score was obtained by analyzing the results to each of the nine questions, using a standardized set of instructions provided by the developers of the index [21]

of operation is a conservative approach, because in such a case the quality of a guideline is possibly not rated as high as it actually is. It may be that many of the processes evaluated by the AGREE instrument were performed but not reported. In these cases transparency of methods is the issue whereas quality may be acceptable. Although none of the guidelines scored well on all the domains, the guidelines of the National Cancer Institute[23] scored relative low compared to the other ones. Important experts in the field developed this guideline, nevertheless an explicit description and justification of the process of developing the guideline was not given within the guideline.
Considering these results one could argue that perhaps the AGREE instrument is too strict. On the other hand however, one could question if guideline developers are aware of the AGREE instrument and its criteria for transparency of guideline development. Given time, the AGREE criteria are likely to become more known and adopted as the need to distinguish between poor and good quality guidelines will increase.
Explicit and detailed information about the objectives and context of the guideline development, including the methods used and the people and organisations involved in the development process are very important. Clinical practice guideline users will have more confidence in guidelines with these elements[24, 25]. Indeed, one could argue that large scale implementation of guidelines is not justified when guideline developers do not report their methods. Therefore, in our opinion, the AGREE instrument is a helpful tool in the process of guideline development and the assessment of guideline quality.
A limitation of this study is that although we used several methods to identify guidelines that were published, there is the possibility that we may have missed some. However, if guidelines were not published in major journals or readily available through the Internet, then most potential users would probably miss them as well. Another limitation of the study is that in assessing the quality of guidelines only the guidelines themselves and relevant documents referred to in the guidelines were used and we did not systematically search for supplementary materials that may have been published elsewhere. However, if users lack clear references and easy access to such background documents, this would be problematic in itself.

The majority of the reviews were non-systematic literature reviews, often referred to as narrative reviews. Such literature reviews are almost always selective, in that they do not involve a systematic, rigorous and exhaustive search of all the relevant literature, using electronic and print media[26] and therefore give only a subjective judgement of the included studies[27].
The 20 systematic reviews of prevention and treatment of oral mucositis published since 2000 represent what should be the highest level of evidence available. One of the major weaknesses of these reviews was that the search strategies reported were not always clear or adequate. The aim of a systematic review is to provide a comprehensive summary of current research evidence. To achieve this aim, a systematic review should employ a transparent and exhaustive search. This may be due to the fact that such reports may not always reflect how the review was actually conducted but only what has been published.

The difficulty in interpreting results strengthens the argument that a systematic review should be a transparent process with the reader of the review being able to identify what has been done.

Conclusion

Although many guidelines on oral mucositis are classified as evidence-based, a profound review of their quality applying the AGREE instrument revealed that none of the guidelines could be recommended. The majority of the guidelines are of middling quality. Also systematic reviews have methodological limitations despite their clinical relevance.

Specific changes must be made at multiple levels by publishers, authors and readers of systematic reviews. First, journals should focus on accepting high-quality systematic reviews and on ensuring that the Methods sections outline the methods in a clearer manner[21].

Authors need to pay particular attention to methods used in systematic reviews, preferably before beginning on this research activity. Finally, readers need to become more familiar with critically appraising systematic reviews and developing a healthy skepticism before incorporating the results into practice.

All the systematic reviews came to the same conclusion that it is important that more well designed, randomised controlled trials are conducted to investigate new treatments for preventing and management of oral mucositis. In line with this we conclude that there is also considerable room for improvement in formulating guidelines as well as systematic reviews for the prevention and treatment of oral mucositis.

Box 2

AGREE Instrument

Response categories for each question are as follows:
1. Strongly disagree
2. Disagree
3. Agree
4. Strongly agree

Scope and Purpose
- The overall objectives of the guideline are specifically described.
- The clinical questions covered by the guideline are specifically described.
- The patients to whom the guideline is meant to apply are specifically described.

Stakeholder Involvement
- The guideline development group includes individuals from all the relevant professional groups.
- The patients' views and preferences have been sought.
- The target users of the guideline are clearly defined.
- The guideline has been piloted among end-users.

Rigor of Development
- Systematic methods were used to search for evidence.
- The criteria for selecting the evidence are clearly described.
- The methods used for formulating the recommendations are clearly described.
- The health benefits, side effects, and risks have been considered in formulating the recommendations.
- There is an explicit link between the recommendations and the supporting evidence.
- The guideline was externally reviewed by experts prior to its publication.
- A procedure for updating the guideline is provided.

Clarity and Presentation
- The recommendations are specific and unambiguous.
- The different options for management of the condition are clearly presented.
- Key recommendations are easily identifiable.
- The guideline is supported with tools for application.

Applicability
- The potential organizational barriers in applying the recommendations have been discussed.
- The potential cost implications of applying the recommendations have been considered.
- The guideline presents key review criteria for monitoring and/or audit purposes.

Editorial Independence
- The guideline is editorially independent from the funding body.
- Conflicts of interest of the guideline development members have been recorded.

Box 3

Review Appraisal Form
The Oxman and Guyatt's index of the scientific quality of research overviews

Reference:
Reviewed by:

1. Were the search methods used to find the evidence (original research) on the primary questions(s) stated?

Yes / Partially (Can't tell) / No

2. Was the search for evidence reasonably comprehensive?

Yes / Partially (Can't tell) / No

3. Were the criteria used for deciding which studies to include in the overview reported?

Yes / Partially (Can't tell) / No

4. Was bias in the selection of studies avoided?

Yes / Partially (Can't tell) / No

5. Were the criteria used for assessing the validity of the included studies reported?

Yes / Partially (Can't tell) / No

6. Was the validity of all studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited?)

Yes / Partially (Can't tell) / No

7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

Yes / Partially (Can't tell) / No

8. Were the findings of the relevant studies combined appropriately relative to the primary question the overview addresses?

Yes / Partially (Can't tell) / No

9. Were the conclusions made by the author(s) supported by the data and/ or analysis reported in the overview?

Yes / Partially (Can't tell) / No

10. How would you rate the scientific quality of the overview?

Extensive flaws		Major flaws		Minor flaws		Minimal flaws
1	2	3	4	5	6	7

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Appendix

Development and testing of the national guideline 'oral mucositis of patients with cancer'

Background

As the primary advocates for patients, nurses are central in preventing and managing oral mucositis and reducing its debilitating effects on patients with cancer. Development of an evidence based guideline for oral mucositis will promote uniformity of care both within a centre, as well as between centres. Furthermore, it will potentially increase the quality of care provided to patients. To meet this challenge, Radboud University Nijmegen Medical Centre, the Dutch Expertise Centre for Nursing (LEVV), the Dutch Research Institute for Healthcare (NIVEL), and the Association of Comprehensive Cancer Centres (ACCC) cooperated to develop a national evidence based guideline. This guideline was based on the results of the study on quality assessment of the methodology used in guidelines and systematic reviews[1]. None of the guidelines met the quality assessment criteria, but eight reviews had an overall Quality Assessment Questionnaire (OQAQ) [2] score ≥ 4 and were eligible for data extraction.

Data extraction

A standardized excel template for data extraction was developed and pre-tested by the reviewers.
The template was based on the information necessary to answer the central questions for guideline development, and divided in three sections: prevention, screening and treatment.
Data were extracted on the general characteristics of the studies (authors, source, year, place, and language of publication); clinical issues (population, intervention and outcomes reviewed), methodological characteristics (language restrictions; number, format, design, and publication status of the studies included; data synthesis; heterogeneity testing; and methodological quality); and results and conclusions.

Analysis

To judge the quality of evidence and the strength of the recommendations of the systematic reviews the GRADE (Grades of Recommendation Assessment, Development and Evaluation)[3] system was used. GRADE proposes the following definitions:

- The quality of evidence; indicates the extent to which one can be confident that an estimate of effect is correct.
- The strength of a recommendation; indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm.

The GRADE working group has developed criteria for assigning the grade of evidence see Box 1[4]. The levels are broken down into four distinct groups: high, moderate, low and very low.
According to the GRADE system high grade evidence is evidence that would not likely

be changed by any future research. Moderate evidence is evidence that may be affected and impacted by future research. This research may change the confidence in the estimate of the truth or may change that estimate altogether. Low grade evidence is evidence that will most likely be influenced and affected by future research and very low quality has an uncertain ability to estimate any effect. Limitations in study quality, important inconsistency of results, or uncertainty about the directness of the evidence can lower the grade of evidence.

None of the guidelines had scores >60% in all domains and none had a score between 30% and 60%, in all domains, indicating low overall quality for all guidelines according to the AGREE Instrument [5]. As no good quality guidelines were identified systematic data extraction was not performed for guidelines and only systematic reviews were included for this purpose.

Box 1: *Grade of evidence*

Criteria for assigning grade of evidence

Type of evidence

Randomised trial = high

Observational study = low

Any other evidence = very low

Decrease grade if:

- Serious (- 1) or very serious (- 2) limitation to study quality
- Important inconsistency (- 1)
- Some (- 1) or major (- 2) uncertainty about directness
- Imprecise or sparse data (- 1)
- High probability of reporting bias (- 1)

Increase grade if:

- Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

Results

Table1 shows the study characteristics of the systematic reviews and contains information describing the quality score of the eight identified systematic reviews, information source, quality assessment used in the reviews, and inclusion criteria for the trials. Interventions for preventing oral mucositis were described in seven reviews, only one review was found to describe interventions for treatment of oral mucositis. All eight reviews formally assessed the methodological quality of the randomised studies included, and few trials were both patient and assessor blinded. No review excluded trials from the analysis because of a too small sample size. Most of the reviews were clear in what types of participants, interventions and outcome measures were included in the review. The total number of studies included in reviews ranged from 7 to 71 with a median of 25 studies per review. Four of the ten reviews conducted a meta-analysis.
Table 2 summarizes key data from 7 reviews of interventions for the prevention of oral mucositis. 44 Interventions divided into 11 groups varying from disinfectants to non-pharmacological or natural agents were investigated. Most interventions failed to prevent oral mucositis. Interventions with some evidence of a benefit in preventing or reducing the severity of oral mucositis included povidone iodine, polymyxin tobramicin amphotericin (PTA) pastilles, benzoydamine, amifostine, cryotherapy, oral care, calcium phosphate rinse, sucralfate, and prostaglandin. However, benefits may be specific for certain types of cancer and its treatment.

Treatment
Table 3 is a summary from the systematic review of Worthington 2006 [6] on 12 interventions explored for treating oral mucositis of which 8 studies dealt with pain control. There is weak and unreliable evidence that allopurinol, polyvariant intramuscular immunoglobulin and human placental extract improves or eradicates mucositis. Oral mucositis can cause severe pain. Given the lack of clear evidence for the treatment or prevention of mucositis, pain control is of utmost importance. Opiates are often required for the relief of mucositis related pain. No evidence was found that patient controlled analgesia (PCA) was better than continuous infusion for controlling pain, despite the fact that less opiates were used per hour with PCA.

There was a considerable overlap across the reviews; for example chlorhexidine was discussed in 4 systematic reviews mostly of the same original studies even though all came to the same conclusion. This was not the case with povidone iodine as 4 reviews discussed this intervention but came to different conclusions.
The GRADE system was used to judge the quality of evidence and the strength of the recommendations of the systematic reviews. Although a very comprehensive method for assessing prevention and treatment modalities, the GRADE system is complicated and difficult to implement in reviews such as the one carried out here. Recommendations were often reached through discussion among the review team.

Table 1: *Overview of included systematic reviews*

Author/Year	QOAQ	Database search	Used quality assessment	Search period	Population	Intervention	Type of study	Outcome
1 Prevention								
Wortington et al.[7]	7	Cochrane Oral Health Group Trials Register Cochrane Central Register Of Controlled Trials MEDLINE EMBASE CINAHL CANCERLITH SIGLE LILACS	Allocation of treatment and information on reasons for withdrawal by trial	1966-April 2004	Anyone with cancer who received chemotherapy and/or radiotherapy.	Active prophylactically agents:	Randomised controlled trials (RCTs)	Mucositis (all levels of severity)
Suterland & Browland[8]	7	Medline. Embase. Cinahl Cancerlit NCI PDQ database	Randomization, blinding, dropouts	1966-June 200	Patients undergoing radiation treatment to the head and neck area	Active treatment	Randomized trials.	Oral mucositis scores, proxy measures of oral mucositis
McGuire et al. [9]	6.5	Medline	A rating form and systematic determination of levels of evidence, based on the American Society of Clinical Oncology criteria	Update 2002-2005	Patients receiving cancer therapy	Basic oral care, bland rinses, protocols and education, good clinical practices	Clinical studies, review studies	Oral condition, cultures of blood, incidence of mucositis, duration mucositis, oral mucositis pain.
Potting et al.[10]	5	Medline, Pubmed, Cinahl, Psycinfo	Randomization, blinding, dropouts	1992-2002	Adult patients with oral mucositis undergoing chemotherapy	Mouthwashes	All randomized studies	Measurement of the severity of mucositis
Migliorati et al.[11]	4.5	Medline	A rating form based on the papers by Hadorn* and Somerfield* to establish the adequacy of each study and then to combine all the studies to provide a level of evidence and grade of recommendation	Update 2002-2005	Not specified in the review, probably cancer patients	Alternative/natural agents, ice or laser therapy	Not specified	Mucositis (not further specified)
Donnelly et al.[12]	4	Medline	Randomization, blinding, dropouts	1964-June 2002	Patients with oral mucositis	Antimicrobial agent	Prospective clinical trials	Incidence of oral mucositis, Severity of oral mucositis, duration of oral mucositis, oral pain

Author/Year	QOAQ	Database search	Used quality assessment	Search period	Population	Intervention	Type of study	Outcome
								Weight loss, type of oral mucositis assessment
Bensadoun et al. [13]	4	Medline	A rating form based on the papers by Hadorn and Somerfield to establish the adequacy of each study and then to combine all the studies to provide a level of evidence and grade of recommendation.	Update 2002-2005	Patients receiving cancer therapy (all kinds, but in results section split into chemo/radio and others	Amifostine	Published peer-reviewed medical literature	Mucositis (complete alimentary tract, but in results split into anatomic region of the alimentary tract: oral mucositis, esophagitis, proctitis, vaginitis)
2 Treatment								
Worthington et al. [6, 14]	7	Cochrane Oral Health Group Trials Register Cochrane Central Register Of Controlled Trials MEDLINE EMBASE CINAHL CANCERLITH SIGLE LILACS	Allocation of treatment, and information on reasons for withdrawal by trial group	1966-August 2003	Anyone with cancer who is receiving chemotherapy and/or radio-therapy and has oral mucositis.	Active agents	Randomised controlled trials	Mucositis at different levels of severity, Days to heal (mean), Oral pain scores or categories Relief of dysphagia Incidence of systemic infection Amount of analgesia Days stay in hospital Cost of oral care Patient quality of life.

QOAQ = overview quality assessment questionnaire, [2]

*Hadorn DC, Baker D, Hodges JS et al Rating the quality of evidence for clinical practice guidelines. J Clin Epidemiol 1996; 49:749–754

* Somerfield MR, Padberg JR, Pfister DG et al ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Class Pap Curr Comments 2000);4:881–

Table 2: *Summary of Systematic reviews of interventions for the prevention of oral mucositis*

Intervention	Source	Included studies*	Patients			Outcome	Quality of evidence
			Chemotherapy	Radio-therapy	Population		
Disinfectants							
Chlorhexidine	Donnelly 2003 Potting 2003 Sutherland 2001 Worthington 2006	17 5 2 7 Total 18	Yes Yes Preparation of RT Yes	Yes No Yes Yes	All All Head/neck All	No difference in OM No difference in OM No difference in OM No difference in OM	Moderate/ Low
Hydrogen peroxide	Sutherland 2003 Potting 2003	1 1 Total 1	Preparation of RT Preparation of RT	Yes Yes	Head/Neck Head/neck	More severe OM No difference in OM	Very Low
Povidone	Donnelly 2003 Potting 2003 Sutherland 2001 Worthington 2006	1 1 1 1 Total 1	No Preparation of RT Preparation of RT No	Yes Yes Yes Yes	Head/neck Not specified Head/neck Head/neck	Less OM Less OM Less sever OM Less OM	Very low
Anti-bacterial							
Clarithromycin	Worthington 2006	1	Yes	No	BMT	No difference in OM	Very low
Iseganan	Worthington 2006	1	No	Yes	Head/neck	No difference in OM	Moderate
Clindamycin	Donnelly 2003	1	Yes	No	HSCT	No difference in OM	Very Low
Anti-viral							
Acyclovir	Worthington 2006	1	No	Yes	Head/neck	No difference in OM	Low
Anti-fungal							
Fluconazole	Donnelly 2003	1	No	Yes	Head/neck lung cancer	No ulcers in patients on prophylaxis	Very low
Combination Anti-bacterial and Anti-fungal							
PTA= Polymyxin, tobramycin, amphotericin.	Donnelly 2003 Sutherland Worthington 2006	5 2 3 Total 5	Yes No No	Yes Yes Yes	Head/neck Head/neck Head/neck	1. Less mucositis/no difference 2. Less severe OM 3. Less OM	Very Low
TCDO=tetrachlorodecaoxide	Donnelly 2003	1	Yes	No	Not specified	No difference in OM	Low

Intervention	Source	Included studies*	Patients			Outcome	Quality of evidence
			Chemotherapy	Radio-therapy	Population		
Tetracycline, nystatin, hydrocortisone, diphenhydramine	Donnelly 2003	1	No	Yes	Head/neck	No difference in OM	Very low
Haematopoietic growth factor							
GM-CSF	Worthington 2006	9	Yes	Yes	All	No difference in OM	Moderate
Keratinocyte	Worthington 2006	1	Yes (5FU)	No	Unknown	No difference in OM	Low
Anti inflammatory							
Prednisone	Worthington 2006	1	No	Yes	Head/neck	No difference in OM	Very low
Benzydamine	Sutherland 2003 Worthington 2006	1 1 Total 2	Preparation of RT Unknown	Yes Yes	Head/neck Head/neck	Less severe OM Less OM	Low
Hydrolytic enzymes	Worthington 2006	2	No	Yes	Head/neck	Less OM mucositis	Low
Antioxidant							
Zinc sulphate	Worthington 2006	1	No	Yes	Head/neck	Less OM	Low
Amifostine	Worthington 2006 Bensadoun 2006	7 13 Total 19	Yes Yes	Yes Yes	Head/neck All	Less OM Inconsistent results, with the majority of the studies showing no difference in OM	Low
Beta-carotene	Sutherland 2003 Worthington 2006	1 1 Total1	No No	Yes Yes	Head/neck Head/neck	No difference in OM No difference in OM	Very low
Non pharmacologic							
Low-energy helium-neon	Sutherland 2003 Migliorati 2006	1 2 Total 2	No Yes	Yes No	Head/neck Unknown	Less OM Non-conclusive results	Low
Cryotherapy	Worthington 2006 Migliorati 2006	2 3 Total 5	Yes (5FU) Yes (melphalan, 5FU)	No No	All HSCT	Less OM Less OM	Moderate
Oral care	Worthington 2006 McGuire 2006	3 2 Total 5	Yes Paediatric	No No	All Unknown	Less OM Less OM Basic oral care including a soft toothbrush with regular replacement	Low
Protocols and education	McGuire 2006	6	Yes	2 studies interviewed staff		Less OM education of patients, families en staff	Very low

Intervention	Source	Included studies*	Patients			Outcome	Quality of evidence
			Chemotherapy	Radio-therapy	Population		
Natural agents							
Honey	Worthington 2006	1	No	Yes	Head/neck	Less OM	Low
Traumeel	Worthington 2006	1	Yes	No	BMT	No difference in OM	Low
Aloe Vera	Worthington 2006 Migliorati 2006	1 1 Total 1	No No	Yes Yes	Head/neck Head/neck	No difference in OM No difference OM	Low
Chamomile	Worthington 2006 Potting 2003	1 1 Total 1	Yes (5FU) Yes	No No	Unknown Unknown	No difference in OM No difference in OM	Low
PV701	Migliorati 2006	1	Yes (BEAM)	No	Unknown	No difference in OM	Very low
Folic acid Folic acid and Vitamin B12	Worthington 2006 Migliorati 2006	1 1 Total 2	Yes (5FU) ??	No ??	Colorectal ??	Induced moderate and severe OM Unclear from review	Low
Multivitamin	Migliorati 2006	1	Yes	No	Breast cancer	No difference in OM	Very low
Vitamin A	Migliorati 2006	1	Paediatric	No	Malignant disease	No difference in OM	Low
Vitamin E	Migliorati 2006	1	No	Yes	Head/neck	Less OM	Low
Miscellaneous							
Calcium phosphate rinse	Worthington 2006	1	Yes	No	HSCT	Less OM	Moderate
Propantheline	Worthington 2006	1	Yes	No	BMT	No difference OM	Very Low
Sucralfate	Sutherland 2003 Worthington 2006 McGuire 2006	5 8 1 Total 11	Preparation of RT Yes No	Yes Yes Yes	Head/neck Head/Neck BMT Head/neck	Less OM Less OM No difference in OM	Moderate
Prostaglandin	Sutherland 2003 Worthington 2006	1 3 Total 4	No Yes	Yes Yes	Head/neck Head/neck BMT	Less OM No difference in OM	Low
Misonidazole	Worthington 2006	1	No	Yes	Head/neck	No difference in OM	Low
Pentoxifylline	Worthington 2006	1	Yes	No	BMT	No difference in OM	Low
Glutamine amino acid	Worthington 2006	5	Yes	Yes	All	No difference in OM	Low
Allopurinol	Worthington 2006	2	Yes (5FU)	No	Unknown	No difference in OM	Low

BMT= bone marrow transplant, HSCT=haemopoietic stem cell transplantation, RT= Radiotherapy

*The total of the original included studies is calculated.

Table 3: *Summary of the systematic review of Worthington-HV, Clarkson-JE, & Eden-OB (2006) Interventions for treating oral mucositis for patients with cancer receiving treatment. The-Cochrane-Library (COCHRANE-LIBR).sitis*

Reference	Intervention	Control	Patients			Outcome		Quality of evidence
			Chemo-therapy	Radio-therapy	Type of cancer	A= Improvement in mucositis B= Mucositis eradicated C= Time to heal mucositis	D= Average pain scores C= Daily mean opiate intake per hour E= Duration of pain control	
Disinfectants								
Dodd 2000	Chlorhexidine Chlorhexidine	Salt/soda Magic: lidocaine diphenhyldramine, aluminium hydroxide	Yes	No	Mixed cancer Leukaemia or BMT	B+C+D: No difference B+C+D: No difference		Moderate
Haematopoietic growth factor								
Hejna 2001	GM-CSF	Povidone-iodine	Yes	No	All	C: No difference		Very low
Papila 2003	GM-CSF	Antimycotic	Yes	No	Head/neck, lung	C: No difference		Very low
Valcarcel 2002	GM-CSF	Saline Solution	Yes	No	BMT	C: No difference		Moderate
Anti Inflammatory								
Kim 1985 Schubert 1988	Benzydamine	Placebo Placebo	No Yes	Yes Yes	Head/neck All	A: No difference		Very Low
Kostrica 2002	Diclofenic	Placebo	No	Yes	Head/neck	D: No difference		Low
Combination Anti-bacterial and Anti-fungus								
Malik 1997	TCDO = tetrachlorodecaoxide	Placebo	Yes (5FU)	No	All	A: No difference		Moderate
Natural Agents								
Kaushal 2001	Human placenta extract	Disprin gargles	No	Yes	Head/neck	A: Statistically significant benefit		Moderate

Reference	Intervention	Control	Patients			Outcome		Quality of evidence
			Chemo-therapy	Radio-therapy	Type of cancer	A= Improvement in mucositis B= Mucositis eradicated C= Time to heal mucositis	D= Average pain scores C= Daily mean opiate intake per hour E= Duration of pain control	
Wadleigh 1992	Vitamin E	Placebo (coconut, soyabean oil)	Yes	No	All	B: No difference		Low
Opium analgesics								
Hill 1992	Alfentanil (PKPCA)	Morphine (PKPCA)	Yes	No	BMT	D: No difference, E: Statistically significant less use		Low
Coda 1997	Sufentanil (PCA) Sulfantanil (PCA)	Morfine (PCA) Hydromoephone (PCA)	Yes Yes	No No	BMT BMT	D: No difference D: No difference		Moderate
Ehrnrooth 2001	Opium	Tricyclic antidepressants	No	Yes	Head/neck	D: Statistically significant benefit		Low
Zucker 1998	Morphine (PCA)	Morphine (staff-controlled)	Yes	No	BMT	D: No difference, E: Statistically significant less use		Very low
Hill 1990 Mackie 1991 Pillitteri 1998	Morphine (PCA) Morphine (PCA) Morphine (PCA)	Morphine (CI). Morphine (CI) Morphine (CI)	Yes Yes Yes	No No No	BMT BMT BMT	1+2+3 = D: No difference, E+F: Statistically significant less use		Low
Hill 1991	Morphine (PA)	Morphine (PKPCA)	Yes	No	BMT	D: No difference, E: Statistically significant less use		Low
Non Pharmacologic								
Syrjala 1992	Therapist support or cognitive-behaviour training or hypnosis.	No training	Yes	No	BMT	D+E: No difference		Very low

Reference	Intervention	Control	Patients			Outcome		Quality of evidence
			Chemo-therapy	Radio-therapy	Type of cancer	A= Improvement in mucositis B= Mucositis eradicated C= Time to heal mucositis	D= Average pain scores C= Daily mean opiate intake per hour E= Duration of pain control	
Syrjala 1995	Therapist support or relaxation and imagery training or cognitive-behaviour training.	No training	Yes	No	BMT	D: No difference		Very low
Miscellaneous								
Porta 1994	Allopurinol	Placebo	Yes (5FU)	No	Colon	A+B+C: Statistically significant benefit		Very low
Schedler 1994	Polyvariant intramuscular immunoglobulin.	Placebo	No	Yes	Head/neck	A: Statistically significant benefit		Low
Chiara 2001	Sucrafate	Placebo	Yes	No	All	A+B: No difference		Low
Loprinzi 1997	Sucrafate	Placebo	No	Yes	Head/neck	B: No difference		Low
Dodd 2003	Sucrafate	Salt/soda	No	Yes	Head/neck	C: No difference		Low

BMT=Bone Marrow Transplant

Expert meeting

To obtain consensus based recommendations where no evidence was available and to discuss the first concept of the guideline an expert group was formed. The group consisted of 12 members: 4 nurses (oncology, haematology radiotherapy, and oncology outpatient clinic), 3 physicians (medical oncology, haematology, and head and neck), a dentist, a dental hygienist, a microbiologist, and two patients who had suffered from oral mucositis. The constitution of this group ensured that clinical experience and patient preferences were properly represented. The first concept guideline was written on the basis of the results of the systematic review. During the expert meeting, the proposed guideline was discussed and adapted and the first draft was then implemented in clinical practice to test its usability. Finally the results of the pilot implementation were discussed in the expert group, where necessary changes and key recommendations were made.

Pilot implementation

The concept guideline was tried out during a period of 3 months and evaluated for its usability by nurses and medical specialists, dentists and dental hygienists. Two university hospitals and two general hospitals participated in the pilot implementation. Several haematological and oncology wards were involved as well as a radiotherapy ward and an outpatient clinic. Nurses on these wards are the potential users of the guideline. The pilot implementation began with an introductory meeting during which participants were given explanations of the guideline and its implementation as well as instructions on oral care. At the end of the period, a questionnaire was used to evaluate the guideline.

Methodology and the content of the guideline

The guideline draft originating from the last expert meeting was presented to external experts who were asked to fill in a form offering their opinion and judgement of the methodology and the content of the guideline. The external experts commented positively on both methodology and validity, and provided some additional remarks. The guideline was adapted and the final draft composed after discussing the external judgment within the project group. Key recommendations are listed in box 2.
This resulted in an evidence-based guideline for screening, preventing and treating oral mucositis of patients treated with chemotherapy with or without radiation therapy. The guideline was disseminated as a book and a summary card for daily use was made. The Dutch Nurses' Association (V&VN oncology) is the owner of the guideline which can be found on digitally www.oncoline.nl.
The next step will be to implement the guideline in all the Dutch hospitals.

Box 2: *Key recommendations*

Key recommendations oral mucositis guideline
Carrying out adequate oral care requires a multidisciplinary team to be available consisting of nurses, physicians, dental professionals and other disciplines.
Before treatment, the oncology team refers the patient to dental professionals to determine the status of the oral cavity and carry out any interventions that may be necessary. • For patients treated with radiotherapy for head and neck cancer or those undergoing haematopoietic stem cell transplantation (HSCT) dental assessment should be performed 2 weeks before cancer treatment • For patients scheduled to undergo other cancer therapies, individual considerations for dental assessment should be made.
Before cancer therapy, nurses should assess the oral cavity to determine the baseline situation so that individual advice can be given to the patient. The nurse takes a history of oral health and inspects the mouth.
Oral care should be carried out to prevent severe oral mucositis among patients treated with chemotherapy, those receiving an HSCT and /or those given radiotherapy in the head and neck region. When necessary, ask for help from a dental hygienist.
The nurse should educate the patient on the importance of good oral care during cancer treatment. This should include: • An explanation of the relation between good oral hygiene and oral complications. • Instructions on rinsing the mouth frequently to remove mucus or food particles. • Plaque prevention. • Prevention of mucosal damage by avoiding hot and spicy food and by being careful with dental prosthesis.
High-risk patients: oral assessment should be done on a daily basis beginning on the day of admission. If this is not possible, estimate oral mucositis by mouth inspection to see if changes of the mucous membrane are visible. Score accordingly.

The nurse instructs the patient on the following aspects of good oral care:

- Dental cleaning method
- Frequency of cleaning: 2-4 times a day
- Toothbrushes: soft, possibly electronic or wet gauzes instead of a brush
- Toothpaste: not irritating, with fluoride, possibly menthol free toothpaste
- Toothbrush hygiene: regular renewal of the toothbrush, drying the toothbrush with the brush upwards.
- In case plaque removal by tooth brushing is not possible, alcohol-free chlorhexidine mouth rinse or spray is indicated.
- Interdental cleaning: only if the patient is accustomed to it and able to carry out the cleaning without damaging the mucosa.
- Frequent rinsing or spraying with water or NaCl 0.9% (radiotherapy 8-10 times a day chemotherapy 4-10 times a day). Rinsing or spraying is indicated after a bout of vomiting. Drinking cold water or sucking on an ice cube can relieve oral pain.
- Lip care: cleaning with a wet gauze and moisturizing with a tube of sterile Vaseline
- Care of dental prosthesis: not wearing the prosthesis at night, but to keeping it in water. In case of oral mucositis dental prosthesis should not be worn.

Provide adequate pain relief: give morphine to patients with pain due to oral mucositis. Use a Visual Analogue Scale (VAS) to determine. Don't use the WHO pain scale. Adjust the dose of morphine daily according to the level of pain

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Chapter 9

General Discussion

One of the aims of this thesis was to describe current nursing practice and practice improvement in relation to oral mucositis directed care in haematology nursing. This was achieved by a survey of European transplant centres, by developing and testing an assessment instrument and by investigating and attempting to improve nurses' skills and knowledge regarding oral care.
The second aim was to evaluate available evidence and guidelines for the preventive care and treatment of oral mucositis in oncology patients in general. This aim was achieved by formulating recommendations for the use of oral mucositis assessment instruments, by investigating the quality of guidelines and systematic reviews for the prevention and treatment of oral mucositis and by developing a national guideline "Oral mucositis in patients with cancer".
This chapter summarises the main findings of this thesis and describes the strengths and limitations of the studies. In addition main conclusions and recommendations for research and practice are given.

Findings towards current practice improvement in haematology nursing care

We surveyed nurses about their perceptions of oral care at European stem cell transplantation centres as they play an important role in assessing and managing oral mucositis (Chapter2). The nurses agreed that oral mucositis has a major influence on the quality-of-life and the costs of care in patients who undergo stem cell transplantation. However, the survey found inconsistencies in the treatment of oral mucositis across centres and identified the need for a more standardised approach. Not all centres provided treatment for patients with grade 4 oral mucositis, a debilitating condition. In contrast, other centres used early intervention and initiated treatment at the first appearance of oral ulcers. The nurses agreed that national evidence-based guidelines should be developed to help standardise the assessment, prevention, and treatment of oral mucositis in European transplantation centres. The results of the survey further demonstrated that fewer than half of the nurses who responded were aware of the newer therapies for oral mucositis.
To observe signs and symptoms of oral mucositis, nurses need assessment instruments. A systematic review was undertaken to summarise the available assessment instruments before developing the Oral Mucositis Nursing Instrument (OMNI) (Chapter3). One of the main findings was that erythema, oedema, lesions, pain and saliva viscosity were the most commonly used items in the various instruments. These items were added together to generate the OMNI to monitor the development, progression and course of oral mucositis. The OMNI was then tested for reliability, usability and responsiveness. With the exception of oedema, the inter-observer Cohen's weighted Kappa of all items was between 0.60 and 0.83. The internal consistency, measured with Cronbach's alpha coefficient, was 0.729, indicating modest, but sufficient internal consistency. Viscosity of saliva contributed little to the OMNI (Spearman's rank-order 0.052)

and were therefore deleted. Usability of the OMNI was good when evaluated with a questionnaire (Chapter 4). Guyatt's responsiveness index was 2.2 and the Receiver Operating Characteristic (ROC) curve was 0.89 for deterioration and 0.92 for improvement, indicating high sensitivity for detecting changes in oral mucositis over time.
In an intervention study, knowledge and skills about oral care improved when education in oral care was provided (Chapter 5). Nursing skills were assessed by reviewing nursing records and observing nurses in performing oral care. Knowledge tests at baseline and follow-up gave an impression of the effect of the education sessions. After the oral care education sessions, knowledge and skills in oral care improved.

Findings towards evidence and guidelines in general oncology care

To guide the assessment of oral mucositis, eleven recommendations were developed based on a systematic review and expert opinion (Chapter 6).
The main recommendations are:

- Oral mucositis should be assessed using a standardised protocol.
- Oral mucositis assessment should continue until oral mucositis is fully resolved.
- Patient reported outcomes should be included in all oral mucositis assessments.
- Oral mucositis assessments should use instruments or combinations of suitable scales containing elements to cover the physical changes in the oral mucosa, functional changes and subjective changes.

In most of the guidelines for the prevention of oral mucositis, patients are advised to rinse their mouth with a mouthwash on a daily basis. A systematic review was performed to assess the effectiveness of commonly used mouthwashes for the prevention of oral mucositis (Chapter7). With the exception of iodine solution, none of the studies investigated were able to demonstrate an effect in preventing mucositis in patients undergoing chemotherapy. The results of all five studies investigating chlorhexidine mouthwashes, when taken together in the analysis, failed to show a significant beneficial effect (Weighted mean differences 0.22; 95% confidence interval CI = -0.20, 0.63). In addition, tooth discolouration and the unpleasant bitter taste experienced by patients supported with the use of sterile water, 9% saline solution or sodium bicarbonate, rather than chlorhexidine.
To identify and assess the quality of available guidelines and systematic reviews for the prevention and treatment of oral mucositis, a systematic review was performed (Chapter 8). Although many guidelines on oral mucositis are classified as evidence-based, a thorough review of their quality using the AGREE instrument revealed that none could be recommended. The majority of the guidelines were of mediocre quality and systematic reviews had important methodological limitations despite their clinical relevance. Consequently, a collaboration of different associations in the Netherlands was established to develop a guideline on oral mucositis. The appendix

with chapter 8 describes the realisation of the evidence based guideline for patients at risk of oral mucositis. The Grade system [1] was used for judging the quality of the evidence and the strength of the recommendations of the systematic reviews. An expert group was set up to obtain consensus recommendations when evidence was lacking.

Strengths and limitations of the studies on practice improvement in haematology nursing care.

Surveying haematology nurses of transplantation centres throughout Europe strengthened the generalisability of the results on current care. It provided a useful insight into the management of oral mucositis in European transplant centres. However, it was sometimes unclear if the answers given by nurses represented the opinion of the transplant centre or their personal views.

A systematic review and extensive testing of the OMNI on validity, reliability, usability and responsiveness are methodological strengths in the development of the assessment instrument. To measure the responsiveness of the OMNI, special statistical techniques had to be employed because the measurements took place on a day-to-day basis which is unique for this kind of instrument. A limitation of the responsiveness study is the small sample size; a larger study will provide more information about the instrument and its use. The instrument was tested in a cohort of haematopoietic stem cell transplant recipients but may be applicable to patients who receive other cancer therapies. Yet, the OMNI was not tested in more general oncology care. For the population of stem cell transplant patients however, the OMNI is a practical instrument for daily nursing practice, and is tested more extensively on methodologically quality than other instruments.

The study on the evaluation of nurses' knowledge and skills in the management of oral care provided direction to the education sessions which met the nurses' need for oral care knowledge. To measure the knowledge of nurses, we were obliged to construct a scale because none was available for our purpose. The clinical relevance of an increase of 50 points on a scale of 0 to 450 points could be debated. However, an increase of approximately 10% could well mean marked improvement in the quality of daily practice. The study was limited by a small sample size, the lack of randomisation and the fact that different nurses participated at baseline and follow-up.

Strengths and limitations towards evidence and guidelines in general oncology care

In this thesis, we performed several systematic reviews (on assessment instruments, mouthwashes, systematic reviews and guidelines) to investigate the evidence for oral mucositis care. As with all systematic reviews, limitations need to be acknowledged.

The quality of the conclusions and recommendations in a systematic review depend on the quality of the studies or trials included. In many areas, the international literature still lacks well designed high quality studies. Despite the extensive search for studies to analyse existing assessment instruments and evidence based recommendations for their use, six out of the eleven recommendations for the assessment of oral mucositis still had to be based on expert opinion. A requirement for systematic reviews is an assessment of the quality of the studies involved. In the study on assessment instruments we did not determine the quality of the studies. Instead, we assessed the quality of the instruments described in these studies. Validity, reliability and usability were the criteria that were used to give an impression of the quality of the instruments. In the review on mouthwashes we did not use a formal quality assessment scale. However, all studies were assessed for randomisation, blinding and intention to treat.

The systematic review of guidelines and systematic reviews was performed in a most thorough manner. The Appraisal of Guidelines for Research and Education (AGREE) instrument was used to assess the quality of the guidelines and the Overview Quality Assessment Questionnaire (OQAQ) was used for the quality of systematic reviews. Both instruments are internationally recognised and validated. The quality of evidence and the strength of the recommendations of the systematic reviews were judged with the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system. The grade methodology was chosen because this was the only method where besides the quality of the involved studies, a balance of advantages versus disadvantages is required. A limitation with the use of GRADE is that this method was not specifically developed for a review of systematic reviews.

A general disadvantage of using systematic reviews is the delay between completion of the inclusion of studies in the review and the time to publication of the review in a journal, which can lead to results being out-of-date. A systematic review of systematic reviews, as carried out in this thesis, suffers even more from this delay. The performance of a meta-analysis was one of the strengths of the systematic review on mouthwashes which showed the ineffectiveness of chlorhexidine in the prevention of oral mucositis. This result was welcomed by nurses as it was in line with nursing practice according to national publications. This evidence is supported and recorded in our national guideline and an international guideline as well [2].

The value of oral assessment in the light of little evidence for interventions

The primary goal of nursing assessment of the oral cavity is to identify changes in the oral mucosa, recognise the presence of infection, and assess the effect that oral mucositis has on patients' functional status. Using systematic, timely oral assessments with a reliable and valid assessment instrument allows oncology nurses to better recognise, monitor, and document the progression of oral mucositis and institute interventions to ease patients' experiences.

The relevance of systematic assessment could be debated in the face of little evidence for nursing interventions for prevention and treatment. However a lack of evidence is not proof of ineffectiveness of interventions such as oral care or patient education. These and similar interventions especially lack good quality evaluations and could still be valuable and possibly supported by more evidence in the future. Also, despite the fact that there are no drugs available for the prevention of oral mucositis, the future is hopeful. A new treatment concept using Palifermin (rHu-KGF1), a keratinocyte growth factor receptor antibody, is now registered for prevention of oral mucositis in autologous hematopoietic stem-cell transplantation patients. A statistically significant improvement of oral mucositis was observed as a result of using Palifermin [3]. Given the effectiveness of Palifermin in the autologous hematopoietic stem-cell transplantation setting, further research is necessary for other indications for the drug, including prevention and reduction of oral mucositis in patients with solid tumours.
As with prevention there is no well-known treatment for oral mucositis. However, nurses can play an active roll in symptom management during this stressful period by providing adequate pain relief, helping patients cope with viscous mucus, paying extra attention to food intake, and offering emotional support.

Validity of findings for subgroups of cancer patients

In the first part of this thesis we discussed several studies that were performed in a haematological setting. It may not be unreasonable to assume, however, that the findings of these studies could be translated into other cancer nursing practices. The survey we undertook, for instance, was based on nurses' perceptions of the management of oral mucositis in Europe and was only sent to transplantation centres. We do not know whether or not the survey is valid for cancer nursing in general.
In the development of the OMNI, a systematic review was undertaken to make an inventory of scoring instruments. In reviewing the literature, there were no limitations in relation to specific patient groups. Therefore it can be assumed that the most relevant items or symptoms (lesions, erythema, oedema, pain, chewing or swallowing) are valid for all patients who suffer from oral mucositis. We tested the OMNI for reliability, usability and responsiveness among HSCT recipients. Therefore, we do not know if the instrument is suitable for patients receiving other therapies for haematological malignancies or other cancer types.
In the second part of this thesis we investigated evidence and guidelines for oral mucositis in general oncology care. There are a number of reliable instruments for evaluating oral mucositis available in the literature designed for various purposes and patients groups. None are universally accepted as they are used for different intentions and populations. However, the recommendations for the use of assessment instruments on oral mucositis are formulated in such a way that they are valid and useful for all patient populations and oral mucositis assessment instruments. By using these recommendations inconsistency will decrease and the quality of oral assessment will improve.

For the development of an evidence-based guideline for oral mucositis, we conducted a systematic review of systematic reviews and guidelines. The approach we used can be applied not only for guidelines and systematic reviews in the area of oral mucositis but for any clinical topic. Eight reviews of sufficient quality were used for data extraction and formed the basis for the national guideline. In searching the literature there were no restrictions regarding patient groups. This resulted in studies performed with various patient groups. In the expert group for the development of a new guideline, most of the disciplines involved in the care for patients at risk of oral mucositis were represented, in order to deliver a guideline for all patients at risk of oral mucositis.
Towards the systematic review on mouthwashes we included only studies where chemotherapy was used as anti cancer treatment. We did not investigate if the recommendations in this review are valid for patients treated with radiotherapy. We concluded that there is no additional value for using chlorhexidine mouth rinses for the prevention of oral mucositis. However, sometimes patients are too sick or oral mucositis is too painful to tolerate tooth brushing 4 times daily. Consequently plaque removal does not take place. In this case an alcohol-free chlorhexidine mouth rinse or spray is could still be considered.

Main conclusions

The first aim of this thesis was to make an inventory of, and to evaluate different aspects of current haematology nursing practice.
With regard to haematology nursing we conclude that nurses should be able to identify chemotherapy induced mucositis as early as possible so that they can intervene to help minimise its severity and evaluate the effectiveness of oral mucositis treatment. The OMNI is a valid, reliable, useable and responsive instrument for this purpose. To optimise the daily assessment nurses must be trained in the use of such a valid, reliable instrument. Assessment of the oral cavity should be started before treatment, and continued after treatment until oral mucositis is fully resolved.
Nurses' knowledge and skills regarding oral mucositis determine the success of prevention and treatment in patients. Regular base education sessions should be provided to nurses, as there is a lack in knowledge and skills. These sessions are probably effective for improving knowledge and skills in daily practice, though education does not automatically result in improved documentation of oral care.
The second aim of this thesis was to evaluate available evidence for preventive care and treatment of oral mucositis and to evaluate guidelines in general oncology care.
Although European oncology nurses believe oral mucositis has a large effect on the patient's quality of life, oral care is not standardised and is inconsistent across Europe.
Current evidence on the prevention and treatment of oral mucositis is incomplete and sometimes inconsistent. Yet, regular oral care is the most commonly mentioned intervention for the prevention and treatment of oral mucositis.
Based on our guideline optimal oral care consists of:

- Baseline oral examination by a dentist before the start of the treatment
- Oral assessment on a regular basis
- Regular tooth brushing and rinsing with water or saline solutions.
- Patient education.

Although the evidence to support the performance of oral care is limited, the importance of oral care is not debated in practice or in the international literature and can be considered to be consensus based.
It is hoped that with the help of the guideline for oral mucositis prevention and treatment, standardized oral care for patients at risk for oral mucositis will be realised.

Recommendations for future research and practice

Assessment is a primary nursing skill. Daily assessment of the oral cavity by nurses permits early recognition of the first signs and symptoms of oral mucositis, interventing when necessary, and evaluating the effectiveness of oral mucositis treatment. Nursing intervention studies on oral mucositis require proper oral assessment with good inter- and intra-observer reliability. Training is necessary to increase the inter- and intra-observer reliability and to standardise the method of scoring. The OMNI should be tested in a group of patients who receive other cancer therapies than haematopoietic stem cell transplantation to determine its generalisability and usability. The OMNI was designed to register the onset and duration of oral mucositis. The daily assessment of the patient's cavity to detect day-to-day deterioration or improvement gives nurses an indication when interventions are needed. Detailed studies on the OMNI should help define the threshold which should trigger specific interventions.
The use of evidence-based guidelines for managing oral mucositis will promote a more informed standard of care and potentially increase the quality of care provided to patients. The foundation of any oral care guideline is basic oral care. However, little evidence can be found in relation to this topic. Therefore, there is a need for more research, investigating components of basic oral care and their effects on oral mucositis. This means there is a need for well designed clinical trials on the effects of patient education and the frequency and optimal nature of daily oral care. Clinical trials are missed in relation to the effects of toothpastes and the use of electronic toothbrushes. There are a considerable number of studies on mouthwashes, yet still some of the most commonly used mouthwashes were not investigated (e.g. there are no studies on NaCl 0.9% or sodium bicarbonate).
Most patients suffer from oral pain caused by mucositis. This pain can be severe, can hinder nutritional intake, cause psychosocial distress and restrict communication [4]. Patients have cited oral pain as a major source of distress [5-7]. The most commonly used pain-relief intervention is pain medication, especially narcotic analgesics. Despite the use of this sort of medications, a majority of patients report only partial relief of pain [4, 5]. The lack of complete relief suggests an ongoing need for multiple strategies in managing patients' pain. Various oral pain assessment strategies and combinations of phar-

macological and non-pharmacological interventions should be investigated in prospective studies.

Standardised and evidence-based guidelines may contribute to a higher quality of nursing care and lead to improved practice and more unambiguous care. Once guidelines are developed, regular updating is necessary to guarantee optimal care based on the latest available knowledge.

Clinical research is consistently producing new findings that may contribute to effective and efficient patient care. The findings of such research will not change patients' outcomes unless health care professionals adopt them in daily clinical practice. Translating research into practice seems as simple as choosing an evidence-based intervention and telling nurses to act on it. To persuade nurses (or other heath- care providers) to start something new however may require different strategies from simply asking them to change their daily routine or to stop something they do frequently. Future research should not only focus on more nursing research but on implementation strategies as well.

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Summary

In this thesis, oral mucositis was examined from a nursing perspective. Oral mucositis is a frequently occurring complication in cancer patients treated with chemotherapy or radiotherapy.
The clinical signs of chemotherapy-induced oral mucositis include erythema, pain, bleeding, viscous or absent saliva and ulceration. Oral mucositis affects speech, the ability to eat or drink or to take oral medication. It can lead to a delay in treatment and has a negative impact on patients' quality of life. Nurses are in the prime position to perform day to day care in patients at risk for oral mucositis, and are vital to its management. Moreover, they are the primary source of information on treatment options for patient. An inventory and an evaluation of different aspects of current nursing practice in the management of oral mucositis are reported in this thesis.

Chapter 1

In the general introduction, background information on the incidence of oral mucositis as a result of different anti-cancer treatments is given. To explain the mechanism by which mucositis occurs, the five phases of Sonis' model of pathophysiology[1] are described and problem areas in current nursing care are discussed.

The aim of this thesis was to:

- describe current nursing practice and practice improvement in relation to oral mucositis directed care in haematology nursing;
- evaluate available evidence for preventive care and treatment of oral mucositis and to evaluate guidelines in general oncology care.

Chapter 2

Oral mucositis is associated with substantial clinical, economic, and quality-of-life (QOL) consequences. The research subgroup of the European Blood and Marrow Transplantation (EBMT) Nurses Group surveyed nurses of transplantation centres for their thoughts about the clinical, QOL, and economic consequences of oral mucositis, the tools for assessing oral mucositis, strategies for preventing and treating oral mucositis and the need for the development and implementation of treatment guidelines. The responses from 46 centres in 16 countries indicated that most nurses (91%) believe oral mucositis has a large impact on patients' wellbeing. Nurses are not very satisfied with current treatments for oral mucositis, but they believe discomfort is reduced by oral care protocols and mouthwashes. Oral mucositis is routinely and frequently assessed, however there are inconsistencies in how it is managed. Most centres (70%) treated all patients with grade 4 oral mucositis, but 9% of the centres did not treat any such patients. In contrast, 33% of the centres treated patients with early stages of oral mucositis at the first appearance of oral ulcers (grade 2 oral mucositis). Most centres used unpublished,

centre-specific guidelines, and the survey found that most nurses agreed that published national guidelines would be valuable for standardising the assessment and management of oral mucositis.

Chapter 3

Chapter 3 describes the development of a new scoring system for the assessment of oral mucositis. The objectives of this study were to summarise the assessment instruments that are available, to develop a new Oral Mucositis Nursing Instrument (OMNI) and to evaluate this new instrument.
A systematic review was undertaken, in which 21 instruments were reviewed and compared. None of the instruments satisfied the criteria for validity and reliability that were established beforehand.
The six most common items from the systematic review were selected for the new instrument. To test the OMNI, pairs of experienced nurses independently assessed the oral cavity of 26 patients. Inter-observer reliability (Kappa), correlations between items (Spearman's rank-order correlations) and internal consistency of the instrument (Cronbach's alpha) were calculated. The usability was evaluated with a questionnaire. Cohen's weighted Kappa's were within an acceptable range. Nearly all correlations were statistically significant and in the predicted direction. The Cronbach's alpha coefficient indicated sufficient internal consistency.
All nurses found the OMNI user-friendly and suitable for day-to-day care.
We concluded that the OMNI can be used as a valid, reliable and usable instrument in nursing practice.

Chapter 4

The OMNI was further tested for responsiveness. Data came from a cohort of 32 recipients of a haematopoietic stem cell transplant unit who had participated in a prospective trial evaluating parenteral glutamine[2]. Evaluations of oral mucositis began between day 7 and 28 after conditioning. Responsiveness was operationalised using two strategies; Guyatt's Responsiveness Index[3] and the Receiver Operating Characteristic (ROC)[4, 5] curves. Guyatt's responsiveness index for the OMNI instrument was 2.2, indicating good sensitivity for detecting changes in oral mucositis over time. The ability of the OMNI to detect day-to-day deterioration (or improvement) was expressed by the areas under the two corresponding ROC curves of 0.89 and 0.92 respectively. The responsiveness of the OMNI suggests it is an appropriate instrument for measuring oral mucositis on a daily basis.

Chapter 5

Good oral care is the most commonly recommended intervention for managing oral mucositis, assuming that nurses have sufficient knowledge and skills to perform oral care correctly.
The aim of the study reported in chapter 5 was to investigate whether knowledge and skills about oral care improve when education in oral care is provided for nurses in charge of patients who are at risk for oral mucositis.
This intervention study consisted of a baseline test on the knowledge and skills of nurses in haematology wards in two different hospitals, followed by oral care education sessions in one of the centres and a follow-up measurement in both centres. At baseline as well as at follow-up, nursing records were examined and observations of nurses performing oral care were made.
The results showed significant differences for scores on the knowledge test before and after the education session for nurses in the intervention setting, whereas there was no difference for the nurses who did not follow these sessions. The records test showed no differences at baseline or follow-up for the two groups. Observations showed that nurses who had attended an education session implemented the oral care protocol considerably better than nurses who did not attend.
The conclusion from the present study was that education in oral care has a positive influence on the knowledge and skills of nurses who care for patients at risk for oral mucositis, whereas documentation of oral care did not improve.

Chapter 6

To assess oral mucositis uniformly, recommendations for the use of assessment instruments are needed.
To address this, a unique collaboration of multi-disciplinary experts from the European group for Blood and Marrow Transplantation (EBMT) and the European Oncology Nursing Society (EONS) was formed. Recommendations were formulated based on a systematic literature review and the experts' experience. Recommendations included a comprehensive baseline assessment and the use of a standardised instrument, or combination of instruments, on a regular basis. Also physical, functional and subjective changes should be measured and subjective measures should be assessed prior to any physical examination. The use of a pain score, in particular patient self-reporting, should be part of any oral mucositis assessment. Any assessment instrument should be validated, easy to use and comfortable for the patient. Finally, the expert group concluded that training of and monitoring in the use of an instrument is vital to successful monitoring of oral mucositis.

Chapter 7

In clinical practice, daily chlorhexidine mouthwash is often recommended to prevent chemotherapy induced oral mucositis[6]. Povidone-iodine, NaCL 0.9%, water salt soda solution and chamomile mouthwash are also recommended. However, the effectiveness of these mouthwashes is unclear. Therefore, a systematic review was performed to assess the effect of mouthwashes on the prevention and severity of chemotherapy-induced oral mucositis. After critical appraisal of study quality, three out of five randomized controlled trials were included in a meta-analysis. The results of the meta-analysis, however, failed to demonstrate a beneficial effect of chlorhexidine when compared to sterile water or NaCl 0.9%. Some patients also complained of tooth discoloration and altered taste. A beneficial effect on the severity of oral mucositis was found for povidone-iodine mouthwash, when compared to sterile water (70% vs. 100% mucositis respectively).

Our results do not support the use of chlorhexidine mouthwash to prevent chemotherapy-induced oral mucositis. Beneficial effects of povidone-iodine mouthwash need further research, also into acceptability for patients.

Chapter 8

The objective of the study reported in chapter 8 was to identify and to assess the quality of evidence-based guidelines and systematic reviews on the prevention and treatment of oral mucositis in patients receiving chemotherapy, radiotherapy or both.

Literature searches were carried out using several electronic databases and websites.

Publications were included if they concerned oral mucositis involving adults treated for cancer and if they had been published after January 1, 2000. As far as systematic reviews are concerned, the article had to report a search strategy, minimally conducted in the databases PubMed or Medline and the articles included in the review had to be subjected to some kind of methodological assessment.

The Appraisal of Guidelines for Research and Education[7] instrument was used to assess the quality of the guidelines and the Overview Quality Assessment Questionnaire (OQAQ)[8] was used to assess the quality of systematic reviews.

31 Articles met the inclusion criteria of which eleven were guidelines and 20 were systematic reviews. The overall quality varied among the different guidelines and reviews. Most guidelines and systematic reviews had serious methodological flaws. Nine of the eleven guidelines did not explicitly describe how they identified, selected and summarised the available evidence. Reviews suffered from lack of clarity, for instance in performing a thorough literature search.

We concluded that there is a need to improve the methodological quality of guidelines and systematic reviews for the prevention and treatment of oral mucositis if they are to be used in clinical practice.

Appendix

Prevention and adequate treatment of oral mucositis is a common task for oncology nurses. The development of guidelines for oral mucositis is essential for nurses taking care of patients who are at risk for, or suffer from oral mucositis. An evidence based guideline will promote uniformity of care within a centre, as well as between centres, and potentially increases the quality of care provided to patients. Several Dutch organisations cooperated to develop such a guideline. This guideline was based on the results of the study on quality assessment of the methodology used in guidelines and systematic reviews [9].

The process of the development of the guideline consisted of several phases:

- Data extraction from eight systematic reviews;
- Expert meetings, to obtain consensus on recommendations when no evidence was available and to develop the guideline;
- Pilot implementation, to test the utility of the guideline; nurses, physicians, oral hygienists and dentists in four hospitals used and evaluated the guideline;
- Appraisal of the methodology and the content of the guideline by external experts.

This resulted in a partly evidence-based and partly expert-consensus-based guideline for screening, prevention and treatment of oral mucositis in patients treated with chemo- and/or radiation therapy. Besides the guideline, a summary card was made for daily practice. The guideline can be found at www.oncoline.nl

Chapter 9

Chapter 9 summarises the main findings of this thesis and describes the strengths and limitations of the studies involved. It further presents the main conclusions that may be drawn and recommendations for further research

The main conclusions are:

- Nurses should assess the oral cavity on daily basis with the help of a standardised protocol;
- The OMNI is a valid, reliable and feasible assessment instrument for daily nursing heamatologic practice;
- Regular oral care education sessions are effective for improvement of nurses knowledge and skills in the area of oral care;
- Patients should receive oral care as described in an evidence and consensus-based guideline;
- The quality of existing guidelines is limited, the National guideline developed from a collaboration in relation to this thesis is based on a more transparent and critical development process and summarises current evidence in this area evidence.

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Samenvatting

Ontsteking van het mondslijmvlies, orale mucositis, komt veelvuldig voor bij patiënten die worden behandeld met chemo- of radiotherapie. Schattingen van de incidentie van mucositis lopen uiteen van rond de 40 procent bij standaard chemotherapie tot meer dan 75 procent van de patiënten die een stamceltransplantatie ondergaan. Nagenoeg alle patiënten die in het hoofd-halsgebied worden bestraald ontwikkelen orale mucositis.
Roodheid, zwelling en pijn zijn de eerste verschijnselen van orale mucositis. Uiteindelijk kunnen er zweren ontstaan die zo pijnlijk zijn dat de patiënt moeite krijgt met spreken, eten en drinken en dus ook moeite heeft om medicijnen te slikken. Dit kan weer tot gevolg hebben dat de behandeling tijdelijk moet worden gestopt. De pijn die patiënten ervaren kan zo hevig zijn dat pijnbestrijding met morfine nodig is. Orale mucositis heeft een sterk negatief effect op de kwaliteit van leven voor deze ernstig zieke patiënten.
Verpleegkundigen geven vierentwintiguurszorg. Zij kunnen dan ook een belangrijke bijdrage leveren aan het voorkomen van ernstige vormen van orale mucositis. Bovendien zijn de verpleegkundigen de eerste bron van informatie over preventie en behandelingsmogelijkheden voor de patiënt.
Dit proefschrift onderzoekt orale mucositis vanuit verpleegkundig oogpunt.

Hoofdstuk 1

In de algemene introductie wordt achtergrondinformatie over de incidentie van orale mucositis gegeven en wordt uitgelegd hoe orale mucositis ontstaat. Daarnaast wordt er beschreven hoe orale mucositis er uitziet en wat dit betekent voor de patiënt. Probleemgebieden in de verpleegkundige zorg worden bediscussieerd. Een goede mondinspectie, om veranderingen vast te stellen en de ernst van de orale mucositis te bepalen, is de eerste belangrijke stap in de behandeling van orale mucositis. Een obstakel hierin is dat er geen universeel geaccepteerd meetinstrument voor handen is om dit gestandaardiseerd uit te voeren. Daarnaast is er onduidelijkheid over de evidence voor preventieve maatregelen en de behandeling van orale mucositis. Bovendien zijn veel maatregelen geen verpleegkundige interventies, maar alleen te gebruiken op doktersadvies. Het is onbekend welke zorg verpleegkundigen nu precies geven aan patiënten die risico lopen op orale mucositis.

Het doel van dit proefschrift is tweeledig:

1. Een inventariseren en evalueren van de hematologische verpleegkundige praktijk in relatie tot orale mucositis en het geven van aanbevelingen om deze te verbeteren;
2. Het evalueren van bestaande evidence voor de preventie en behandeling van orale mucositis en het evalueren van richtlijnen in de algemene oncologische zorg.

Hoofdstuk 2

De verpleegkundige onderzoekssubgroep van de European Group for Blood and Marrow Transplantation (EBMT) heeft onderzoek gedaan naar de mening van verpleegkundigen over de verpleegkundige aspecten van orale mucositis (OM). In de vragenlijst werd gevraagd naar hun mening over de klinische en economische consequenties van OM en gevolgen die OM heeft voor de kwaliteit van leven van patiënten. Tevens werden er vragen gesteld over de gebruikte meetinstrumenten om de ernst van OM te registeren, strategieën voor de preventie en behandeling van OM en de behoefte aan ontwikkeling en implementatie van richtlijnen. Verpleegkundigen van 46 transplantatie centra uit 16 Europese landen hebben de vragenlijst ingevuld. De meeste verpleegkundigen (91%) vinden dat OM een grote impact heeft op het welbevinden van de patiënt. Verpleegkundigen zijn niet tevreden met de bestaande behandelingsmogelijkheden, maar geloven wel dat het ongemak dat patiënten ervaren kan worden verminderd door het geven van goede mondverzorging en het gebruik van mondspoelmiddelen. Ondanks het feit dat OM vaak voorkomt, bestaan er diverse verschillen in de behandeling van OM. In de meeste centra (70%) ontvangen patiënten met ernstige OM (graad 4 WHO) een behandeling, maar in 9% van de centra gebeurt dat niet. Aan de andere kant start 33% van de centra hun behandeling al bij de eerste verschijnselen van OM. De meeste centra gebruiken eigen, centra- specifieke richtlijnen. Verpleegkundigen uit deze centra zijn van mening dat meer algemene (nationale) richtlijnen voor OM de zorg en behandeling van de betreffende patiënten kunnen standaardiseren en verbeteren.

Hoofdstuk 3

Hoofdstuk 3 beschrijft de ontwikkeling van een nieuw meetinstrument voor de beoordeling van orale mucositis. Allereerst werd er een systematisch literatuur onderzoek verricht naar bestaande meetinstrumenten. Hierbij werden 21 meetinstrumenten gevonden en bekeken op validiteit, betrouwbaarheid en bruikbaarheid. Een op alle onderdelen geschikt meetinstrument werd niet gevonden.
De Oral Mucositis Nursing Instrument (OMNI) werd vervolgens ontwikkeld op basis van de zes meest voorkomende items uit het literatuuronderzoek. De OMNI werd in een hematologische context getest door paarsgewijs ervaren verpleegkundigen onafhankelijk van elkaar de mond van 26 patiënten te laten beoordelen. De interrater betrouwbaarheid, correlatie tussen de items en de interne consistentie van het instrument als geheel werden hierbij berekend. De bruikbaarheid van het instrument werd geëvalueerd met behulp van een vragenlijst. De betrouwbaarheid van het instrument bleek voor de diverse onderdelen voldoende tot goed . De verpleegkundigen vonden de OMNI gebruiksvriendelijk en bruikbaar voor de dagelijkse praktijk.
Hieruit kan geconcludeerd worden dat de OM een valide, betrouwbaar en bruikbaar meetinstrument is voor de verpleegkundige zorg bij hematologische patiënten.

Hoofdstuk 4

Een meetinstrument moet responsief zijn, dat wil zeggen, een meetinstrument moet in staat zijn om klinische veranderingen te constateren.
Om de OMNI te testen op responsiviteit werd het instrument uitgetest bij 32 stamceltransplantatiepatiënten. De evaluatie van orale mucositis startte op dag 7 van de behandeling en stopte op dag 28. Gedurende al deze dagen werd het beloop van orale mucositis met de OMNI gevolgd.
De responsiviteit werd afgezet tegen het beloop volgens de Daily Mucositis Score (DMS) en op 2 manieren berekend. De Guyatt's Responsiveness Index voor de OMNI bleek 2.2 te zijn, wat betekent dat het instrument gevoelig is om veranderingen in orale mucositis in de loop van de tijd te detecteren. De mogelijkheid van de OMNI om van dag tot dag verslechteringen of verbeteringen van orale mucositis te constateren werd daarnaast berekend met behulp van Receiver Operating Characteristic (ROC) curve. Ook de ROC curve toonde aan dat de OMNI veranderingen van dag tot dag detecteert.
Geconstateerd kan worden dat de OMNI bij toepassing voor stamceltransplantatiepatiënten een responsief instrument is.

Hoofdstuk 5

In de literatuur is de meest genoemde aanbeveling voor de preventie en behandeling van orale mucositis goede mondzorg, er van uitgaande dat verpleegkundigen voldoende kennis en vaardigheden hebben om deze zorg goed uit te voeren.
Het doel van de studie in hoofdstuk 5 was om te inventariseren of kennis en vaardigheden van verpleegkundigen met betrekking tot mondzorg verbeteren wanneer extra lessen in mondverzorging gegeven worden. Deze interventiestudie bestond uit een nulmeting van kennis en vaardigheden bij verpleegkundigen die werkten op hematologische afdelingen in twee verschillende ziekenhuizen. De lessen in mondzorg werden gegeven in één van de twee ziekenhuizen, de afdeling in het andere ziekenhuis fungeerde als vergelijkingsgroep. Vervolgens vond de nameting plaats in beide ziekenhuizen. De metingen bestonden uit een kennistest, observaties tijdens de uitvoering van mondzorg en dossieronderzoek.
Er werd een significant verschil gevonden in de scores op de kennistest voor en na de mondzorglessen in de interventiegroep, terwijl er geen verschil gevonden werd in de groep verpleegkundigen die geen mondzorgles hadden gehad. De dossiercheck toonde geen verschil tussen de nulmeting en de nameting voor beide groepen. De observaties toonden aan dat verpleegkundigen die de lessen hadden gevolgd het mondverzorgingsprotocol beter uitvoerden dan verpleegkundigen geen les hadden gehad.
De conclusie van deze studie is dan ook dat mondzorglessen een positieve invloed hebben op de kennis en vaardigheden van hematologieverpleegkundigen die zorgen voor patiënten die risico lopen op orale mucositis.

Hoofdstuk 6

Om uniformiteit te verkrijgen in het evalueren en beoordelen van orale mucositis zijn er richtlijnen nodig die aangeven hoe meetinstrumenten gebruikt moeten worden. Om dit te bereiken werd een multidisciplinaire groep samengesteld die bestond uit experts van twee Europese organisaties: de European Group for Blood and Marrow Transplantation (EBMT) en de European Oncology Nursing Society (EONS). Aanbevelingen werden geformuleerd op basis van een systematisch literatuuronderzoek en op basis van de expertise van de experts. De aanbevelingen omvatten een uitgebreide basisevaluatie en het regelmatige gebruik van een gestandaardiseerd meetinstrument of een combinatie van meetinstrumenten. Het gebruikte meetinstrument moet de mogelijkheid geven tot het evalueren van objectieve, subjectieve en functionele veranderingen. Het instrument dient valide te zijn, eenvoudig in het gebruik en comfortabel voor de patiënt. Het beoordelen van de mate van pijn bij de patiënt hoort deel te zijn van elke meeting. Tenslotte concludeert de expertgroep dat training in het gebruik van een meetinstrument van vitaal belang is om orale mucositis correct te evalueren.

Hoofdstuk 7

In de klinische praktijk wordt het dagelijkse gebruik van chloorhexidine als mondspoelmiddel vaak aanbevolen voor de preventie van chemotherapiegeïndiceerde orale mucositis. Ook jodiumoplossing, NaCl 0.9%, een oplossing van zout en soda en kamillemondspoelmiddel worden vaak aanbevolen. De effectiviteit van deze mondspoelmiddelen is echter niet duidelijk. Daarom werd in een systematisch literatuuronderzoek nagegaan of deze mondspoelmiddelen bijdragen aan de preventie van orale mucositis.
Na een kritische beoordeling van de kwaliteit van de geïncludeerde studies kwamen drie van de vijf studies die chloorhexidine onderzochten ter preventie van mucositis in aanmerking voor opname in een meta-analyse. Het resultaat van de meta-analyse liet geen significant effect zien voor chloorhexidine ten opzichte van steriel water of NaCl 0.9%. Een aantal patiënten in de studies klaagde over tandverkleuring en een onaangename bittere smaak bij gebruik van chloorhexidine.
Onderzoek naar het gebruik van jodiumoplossingen is zeer beperkt, maar liet wel een positief effect zien voor dit middel. Op basis van onze bevindingen kan het gebruik van chloorhexidine als mondspoelmiddel ter preventie van chemotherapiegeïndiceerde orale mucositis niet worden aanbevolen. Het gebruik van jodiumoplossing verdient nader onderzoek.

Hoofdstuk 8

Het doel van de studie in hoofdstuk 8 was het identificeren en beoordelen van de kwaliteit van richtlijnen en systematische reviews gericht op de preventie en behandeling van orale

mucositis bij patiënten die behandeld worden met chemotherapie en/of radiotherapie.
Voor het zoeken van literatuur werden verschillende databases en websites geraadpleegd. Richtlijnen en systematic reviews werden geïncludeerd wanneer het orale mucositis betrof bij volwassen patiënten die behandeld werden voor kanker en wanneer deze gepubliceerd waren na 1 januari 2000. De systematische reviews moesten minimaal een zoekstrategie beschrijven, minimaal moest er gezocht zijn in de databases PubMed of Medline en de artikelen in de review moesten methodologisch beoordeeld zijn. Om de kwaliteit van de richtlijnen te beoordelen werd het Appraisal of Guidelines for Research and Education (AGREE) instrument gebruikt. Om de kwaliteit van de systematisch reviews te beoordelen werd de Overview Quality Assessment Questionnaire (OQAQ) gebruikt.
31 Bronnen werden geïncludeerd waarvan 11 richtlijnen en 20 systematische reviews.
De kwaliteit varieerde sterk tussen de verschillende richtlijnen en systematische reviews. De meeste richtlijnen en systematische reviews hadden serieuze methodologische tekortkomingen. Negen van de elf richtlijnen beschreven bijvoorbeeld niet expliciet hoe zij de gevonden evidence hadden geïdentificeerd, geselecteerd en samengevat. Op basis van deze resultaten en andere resultaten kon worden geconcludeerd dat de methodologische kwaliteit van richtlijnen en systematische reviews voor de preventie en behandeling van orale mucositis sterk verbeterd kan worden.

Appendix

Waar hoofdstuk 8 de kwaliteit van bestaande richtlijnen en systematic reviews kritisch belicht, wordt in het appendix toegelicht hoe op basis van de beoordeling van de gevonden systematic reviews een nieuwe richtlijn voor de preventie en behandeling van orale mucositis werd ontwikkeld. Het nemen van preventieve maatregelen en het inzetten van adequate zorg voor de behandeling van orale mucositis behoren immers tot de taken van oncologieverpleegkundigen maar de studie in hoofdstuk 8 toonde ook aan dat een geaccepteerde, met actuele kennis onderbouwde richtlijn ontbreekt hiervoor ontbrak. Om een (landelijke) richtlijn tot stand te brengen werd er een multidisciplinaire werkgroep van experts samengesteld.
De ontwikkeling van de richtlijn bestond uit een aantal fases:

- Data extractie van acht systematische reviews
- Expertbijeenkomsten om op consensus gebaseerde aanbevelingen te formuleren daar waar geen evidence voor handen was en om het eerste concept van de richtlijn te bediscussiëren.
- Pilot-implementatie om de bruikbaarheid van de richtlijn te testen. Verpleegkundigen, artsen, mondhygiënisten en tandartsen gebruikten en evalueerden de richtlijn.
- Beoordeling van de methodologische kwaliteit en de inhoud van de richtlijn door externe experts.

Dit alles resulteerde in een evidence-based richtlijn voor de preventie en behandeling van orale mucositis.

Hoofdstuk 9

In hoofdstuk 9 worden de algemene bevindingen van dit proefschrift samengevat, de sterke en de zwakke punten van de betrokken studies worden besproken. Daarnaast worden de belangrijkste conclusies beschreven en aanbevelingen voor toekomstig onderzoek gegeven.
De belangrijkste conclusies zijn:

- Verpleegkundigen moeten bij patiënten met risico op orale mucositis dagelijks een mondinspectie uitvoeren met behulp van een gestandaardiseerd protocol;
- Mondzorglessen zijn effectief bij het verbeteren van kennis en vaardigheden van verpleegkundigen bij het uitvoeren van mondzorg;
- Patiënten moeten mondzorg ontvangen zoals die beschreven is in evidence en consensus gebaseerde richtlijnen;
- De kwaliteit van bestaande richtlijnen is beperkt. De nieuwe nationale richtlijn, die in een samenwerkingsverband is ontwikkeld en is gebaseerd op een transparant en kritisch ontwikkelingsproces, beschrijft de bestaande evidence uitgebreid en nauwkeurig.

Dankwoord

Dankwoord

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Mijn moeder overleed nog voordat ik met dit promotietraject begon. Mijn vader overleed 2 jaar geleden. Pap en mam, wat zouden jullie trots geweest zijn. Maar ik weet dat mijn broers en zussen plaatsvervangend trots zullen zijn.

Curriculum vitae

Curriculum Vitae

Carin Potting is geboren op 15 september 1956 te Meerssen. Na het behalen van haar HAVO diploma in 1975 op de scholengemeenschap Stella Maris te Maastricht startte zij met de inservice opleiding in het St. Radboud ziekenhuis te Nijmegen. Na de afronding (1979) behaalde zij de kinderaantekening en dialyse-aantekening. Vervolgens heeft zij als verpleegkundig teamleider 18 jaar op de afdeling kinderdialyse in het UMCN St. Radboud gewerkt. Tijdens deze periode was zij gedurende 6 jaar bestuurslid van de European Dialysis and Transplant Nurses Association/European Renal Care Association (EDTNA/ERCA). Daarnaast studeerde zij in deeltijd Gezondheidswetenschappen.
Na haar afstuderen werd Carin beleidsmedewerker functiedifferentiatie voor het Cluster Inwendige Specialismen (CIS) en verpleegkundig onderzoeker op de afdeling hematologie in het UMCN St. Radboud.
De klinische afdeling hematologie heeft een onderzoekslijn Supportive Care. Het medisch onderzoek naar Mucosal Barrier Injury is hierbinnen een belangrijke peiler. Het verpleegkundig onderzoek naar orale mucositis is een waardevolle aanvulling. Naast het verzorgen van gastcolleges op de HAN en de complementmodule hematologie geeft zij presentaties op het gebied van orale mucositis op congressen. Carin is lid van het research sub-committee van de European Group for Blood and Marrow Transplantation Nurses Group. Daarnaast is zij is lid van de Nursing Advisory Board of the Myelodysplastic Syndromes Foundation.